CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105187

Kidney and heart damage associated with high blood pressure: strategies for early detection in primary care settings

Daños renales y cardiacos asociados a la hipertensión arterial: estrategias para su detección precoz en el ámbito de la atención primaria

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Keywords:
High blood pressure, kidney damage, heart damage.

Palabras clave:
Presión arterial alta, daño renal, daño cardiaco.

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ABSTRACT

High blood pressure (HBP) is a highly prevalent metabolic condition in the Mexican population that produces multisystem involvements with heterogeneous effects among individuals. In the long term, the complex relationship between cardiometabolic risk factors promotes the development of Atherosclerotic Cardiovascular Disease (ASCVD). A critical associated complication is the cardiorenal effect related to HBP, which leads to a high burden of chronic kidney disease (CKD) and heart damage. Hence, the importance of promptly identifying cardiorenal impairments at early stages of the disease within primary care (PC) personnel. This work aims to point out the early diagnosis strategies for kidney and heart damage in patients with HBP to systematize their search in a PC setting. A moderate decrease in the estimated glomerular filtration rate (eGFR) and the presence of any degree of albuminuria are excellent markers for screening kidney damage. Left ventricular hypertrophy (LVH) assessed with either an electrocardiogram (EKG) or echocardiography had well-defined criteria and validated indexes to identify cardiac damage. Finally, a severe complication is heart failure (HF), which needs to be fundamentally based on clinical and EKG findings. A correct interpretation of an EKG makes an accurate diagnosis in 75% of patients living with HF. The proper implementation of these strategies in a PC scenario is crucial to identify cardiorenal impairments and reduce the long-term incidence of ASCVD in the Mexican population.

RESUMEN

La hipertensión arterial (HTA) es una condición metabólica de alta prevalencia en la población mexicana que produce afectaciones multisistémicas con efectos heterogéneos entre los individuos. A largo plazo, la compleja relación entre los factores de riesgo cardiometabólico promueve el desarrollo de la enfermedad cardiovascular ateroesclerótica (ECAE). Una complicación crítica asociada es el efecto cardiorrenal relacionado con la HTA, que conduce a una alta carga de enfermedad renal crónica (ERC) y daño cardíaco. De ahí la importancia de identificar con prontitud las alteraciones cardiorrenales en las fases iniciales de la enfermedad en el personal de atención primaria (AP). Este trabajo pretende señalar las estrategias de diagnóstico precoz del daño renal y cardíaco en pacientes con HTA para sistematizar su búsqueda en el ámbito de la AP. La disminución moderada de la tasa de filtración glomerular estimada (TFGe) y la presencia de cualquier grado de albuminuria son excelentes marcadores para detectar el daño renal. La hipertrofia ventricular izquierda (HVI) evaluada con un electrocardiograma (EKG) o una ecocardiografía tenía criterios bien definidos e índices validados para identificar el daño cardíaco. Por último, una complicación grave es la insuficiencia cardíaca (IC), que debe basarse fundamentalmente en los hallazgos clínicos y del electrocardiograma. Una correcta interpretación del electrocardiograma permite realizar un diagnóstico preciso en 75% de los pacientes con IC. La implementación adecuada de estas estrategias en un escenario de AP es crucial para identificar las alteraciones cardiorrespiratorias y reducir la incidencia a largo plazo de la ECAE en la población mexicana.

How to cite: Palomo-Piñón S, González-Coronado VJ, Antonio-Villa NE. Kidney and heart damage associated with high blood pressure: strategies for early detection in primary care settings. Cardiovasc Metab Sci. 2022; 33 (s3): s216-s222. https://dx.doi.org/10.35366/105187

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Abbreviations:
ASCVD = Atherosclerotic Cardiovascular Disease.
CKD = Chronic Kidney Disease.
PC = Primary Care.
CVD = Cardiovascular Disease.
HF = Heart failure.
ESRD = End-stage renal disease.
CV = Cardiovascular.
eGFR = Estimated glomerular filtration rate.
MACE = Mayor Cardiovascular Event.
ACR = Urinary albumin-creatinine ratio.
LVH = Left ventricular hypertrophy.
LV = Left ventricle.
HFpEF = Preserved ejection fraction.
HFrEF = Reduced ejection fraction.
HR = Hazard Ratio.
LR = Likelihood ratio.

INTRODUCTION

High blood pressure (HBP) has been recognized as significant risk factor for the development of cardiovascular diseases (CVD).[1] Its importance relies on its silent and hazardous manifestations in target organs such as the heart, cardiovascular system, and kidneys. At a public health level, strategies to diminish the burden of HBP, with an appropriate diagnosis and treatment to prevent complications in the long term have been developed. Nevertheless, Mexico is distinguished to have a high prevalence of undiagnosed and untreated HBP. The most recent evidence conducted from a sub-analysis of the May Measure Month 2019 at the Eastern zone in Mexico revealed an estimated prevalence of HBP of 32.4%. The same study reported that the proportion of patients without diagnosis and treatment was 28.3%.[2] At an individual level, HBP's systemic damage is translated into Atherosclerotic Cardiovascular Disease (ASCVD) with heterogeneous and diverse effects in magnitude among individuals, which is translated into cardiorenal associated diseases. Unstable angina, heart failure (HF), multivessel disease, CKD, and cerebrovascular disease are entities which have been posed to be severe cardiorenal complications related to HBP. Nevertheless, the detection, management, and treatment of cardiorenal diseases are often challenging in Primary Care (PC) settings due to limited resources, lack of advanced diagnostic elements, and awareness of healthcare workers for its systematically screening. Hence, there is a need to comprehend and understand current strategies to detect and screen cardiorenal associated complications early in a PC scenario. This work aims to detail a brief review of the current diagnosis strategies to screen kidney and heart damage in a PC scenario to help further its diagnosis, management, and prompt referral to specialized care setting.

Kidney damage

Pathophysiological pathways related to kidney injury attributable to HBP are complex. It has been recognized that increased blood pressure leads to microscopic impairments in glomerular capillaries in the nephron which overstimulate the renin-angiotensin-aldosterone system. This essentially creates hemodynamic impairments which favor non-hemodynamic changes. Both phenomena create a perfect environment to promote further cascades that consequently lead to a cardiorenal system injury. The interplay between hemodynamic and non-hemodynamic pathways has a bidirectional effect, which is translated into a higher incidence of CKD in patients living with HBP in patients with CKD.[3]

Glomerular filtration rate

It has been estimated that HBP is the second leading cause of end-stage renal disease (ESRD) in Mexico. Notably, ESRD is a strong predictor of cardiovascular (CV) morbidity and mortality. It has been proposed that the estimated glomerular filtration rate (eGFR) and albuminuria are the most appropriate and precise indicators to evaluate the extent and degree of kidney damage in patients living with HBP.[3] A moderate decrease in eGFR (GFR < 30 mL/min/1.73 m^2) and the presence of any degree of albuminuria are unequivocal signs of kidney damage. *Table 1* describe the values for each one.[4]

A study performed by Mafham et al. demonstrated that for every 20 mL/min/1.73 m^2 reduction of eGFR, the risk of presenting a fatal or non-fatal major cardiovascular event (MACE) increases by approximately 50%.[5] Laboratory measurements are needed to give an accurate approximation for the eGFR. The

Table 1: Categories of glomerular filtration rate and albuminuria.

GFR categories (mL/min/1.73 m^2)	Description	Range
G1	Normal or high	≥ 90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Mildly to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	< 15
Persistent albuminuria categories		
A1	Normal to mildly increased	< 30 mg/g < 3 mg/mmol
A2	Moderately increased	30-300 mg/g 3-30 mg/mmol
A3	Severely increased	> 300 mg/g > 30 mg/mmol

Modified from: KDIGO 2012. Shlipak MG et al.[4]

most used and widely available are biomarkers are Serum Creatinine and Cystatin C, which then are applied to online-based equations for its interpretation. The most used equations are CKD-EPI and MDRD-4 (https://www.senefro.org/modules.php?name=calcfg), which consider essential aspects of the patients, such as the body surface, age, and ethnicity, to give an adjusted and expressed eGFR expressed on the surface of an average-sized person by 1.73 m^2. The Cockcroft-Gault formula is another important equation, which is weight-based and gives an estimated Creatinine Clearance; the Cockcroft-Gault formula has shown a better performance in subjects with mild or moderate renal function impairment, whereas CKD-EPI and MDRD can be used at any level of renal function. Although not achieving maximum precision, recent studies indicate that CKD-EPI could reduce bias and give a better estimation for the eGFR compared to MDRD-4.[6] Nevertheless, these equations should be interpreted with caution within certain circumstances, as it has been reported that body composition impairments could alter creatinine production, such as patients living with obesity, malnutrition, or cachexia, and in consequence, give inaccurate eGFR estimations. In these cases, the eGFR assessment should not be adapted to 1.73 m^2, with the objective to avoid its overestimation; consequently, its absolute value should be used. This same concern applies to the Cockcroft-Gault equation. Therefore, limitations and caution are awarned while using these formulas within these contexts.

Albuminuria

Another universally accepted marker to evaluate renal manifestation for generalized endothelial dysfunction is albuminuria, which is a strong predictor of progression to ESRD in subjects living with and without diabetes. The PREVEND study (Prevention of Renal and Vascular End-stage Disease Study), was one of the first studies that reported an estimated prevalence of albuminuria in healthy population of 6.6%, which increased to 7.2% in patients living with HBP or diabetes. Furthermore, the same study reported that even in healthy populations, its continuous excretion has a well-documented relationship with CV risk, as people with normal Albuminuria values (10-20 mg/L or 15-30 mg/24 h), had an increased CV risk compared with those without albuminuria.[7] Depending on the studied cohort, the worldwide prevalence of kidney damage in subjects living with HBP

varies from 5 to 60%.[3] However, in Mexico, the information for this topic is limited. Available data indicates that approximately 12% of the population living with HBP and diabetes have an eGFR ≤ 60 mL/min/1.73 m^2 and albuminuria > 30 mg/g.[8] According to the latest recommendations of KDIGO 2021, it is preferable to measure albuminuria instead of proteinuria since albuminuria helps to stratify the risk of progression to ESRD and makes an adequate stratification of renal function.[4] The estimation of albuminuria is highly reliable when measured using semi-quantitative methods, such as test strips or immunological methods in the laboratory. Nevertheless, the test strips are the most affordable and widely available method in PC settings. It has been reported that test strips have a sensitivity of 80-97% and a specificity of 33-80%, making them a good strategy for initial screening and follow-up. Finally, recent data indicate a more comprehensive approach involves using the Albumin/Creatinine Ratio (ACR), where a threshold of > 30 mg/g is considered abnormal. Regarding the scarce information from Mexico, there is no doubt that measurement of eGFR and detection of albuminuria should be crucial strategies in PC settings, as both indicators could lead to a prompt treatment to decrease CV risk in patients living with HBP.

Heart damage

The heart is a crucial organ that experiences impairments within its structure and functionality closely related with other organs, such as the kidney. Briefly, the increased tension and post-charge hemodynamic forces increases within higher HBP stages. These changes within the cardiovascular system, lead towards a progressive increase in myocardial tissue and enlargement in left ventricle, which ultimately ends in left ventricular hypertrophy (LVH).[9] The consequences have been described as progressive HF, as well as a thickening of the intima-media in carotids, which are also correlated with kidney damage. Both heart and kidney damage are conditioning the promote a higher incidence of CV events.[10]

Left ventricular hypertrophy

Variants which are described for LVH are concentric and eccentric hypertrophy and concentric remodeling. These variants predict an increased incidence of ASCVD and adverse renal outcomes. It has been described that concentric hypertrophy is the most consistent independent CV risk factor, as it increases ≥ 20% the risk for any MACE in 10 years.[11] Therefore, the presence of LVH is the most consistent marker of cardiac injury. The initial screening method to evaluate LVH is through an electrocardiogram (EKG). There are well-defined EKG criteria that have been correlated against more sophisticated methods such as echocardiography, magnetic resonance imaging, and histopathological samples. In *Table 2*, we present the most used EKG criteria (Sokolow-Lyon, Cornell, and Lewis's Indexes) which could help to identify the presence of LVH in a PC scenario.[12] The Sokolow-Lyon Index continues to have the highest sensitivity and specificity to identify LVH validated with

Table 2: Electrocardiographic criteria based on voltage.

Indexes	Formulas	EKG criteria
Sokolow-Lyon	S V1 + R V5 o R V6	≥ 3.5 mV = 35 mm
	R aVL	> 1.1 mV = 11 mm
Cornell	R aVL + S V3	H: ≥ 2.8 mV = 28 mm
		M: ≥ 2 mV = 20 mm
Lewis	(R D1 + S D3) – (R D3 + S D1)	> 1.7 mV = 17 mm

Modified from: Tsioufis C et al,[11] Rolon-Acosta et al.[12]

Table 3: Echocardiographic criteria by sex for left ventricular hypertrophy.

	Women			Men		
Markers of LVH	Mild	Moderate	Severe	Mild	Moderate	Severe
Thickness of the septum	10-12	13-15	≥ 16	11-13	14-16	≥ 17
Thickness of the posterior left ventricular wall	10-12	15-16	≥ 16	11-13	14-16	≥ 17

Data expressed in mm. Modified from: Tsioufis C et al,[11] Rolon-Acosta et al.[12]

echocardiogram imaging (Specificity: 83%; Positive Predictive Value: 85%, Likelihood Ratio: 2.28).[13] Other available indexes are the Novacode and the Romhilt-Estes.[9] Nevertheless, it has been reported that in obese subjects, the use of the Sokolow-Lyon Index, along with the Cornell index had reduced sensitivity and specificity; therefore, caution should be taken when using these markers to identify LVH.

Echocardiography

Echocardiography is a highly precise imaging technique which provides information on the structure and geometry of the left ventricle (LV), systolic and diastolic function, and other coexisting cardiac alterations. It is the most used method to assess follow-up pharmacological management of LVH. Nevertheless, its availability in PC scenarios in Mexico continues to be limited and insufficient.[9] *Table 3* describes the echocardiographic values to diagnose and stratify LVH by sex. Nevertheless, whether the reduction of LVH could provide long-term cardio-nephroprotection is an area of opportunity for further study.[11]

Heart failure

Heart failure (HF) is considered a long-term consequence of hypertensive heart disease. According to the Framingham Heart Study, approximately 39% of men and 59% of women living with HBP will develop HF.[13] In most patients, LV diastolic dysfunction is the first clinical manifestation, presenting with a preserved (HFpEF) or reduced (HFrEF) ejection fraction. Its terminal phase is characterized as a dilated cardiomyopathy with diastolic dysfunction and reduced ejection fraction. The diagnosis is usually made in the advanced stages: the patient who is diagnosed by dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, rales, ankle edema, third heart sound/gallop, jugular venous distension with or without hepatomegaly and sinus tachycardia at rest, has little chance of regaining his quality of life. Therefore, it is necessary to diagnose HF in early stages in PC settings, when it is asymptomatic, to reduce its associated morbidity and mortality. When HF progresses, a phenomenon is known as «decapitated hypertension» occurs, where blood pressure decreases to even low levels and represents a therapeutic challenge.[14]

The appropriate diagnosis of HF is based on clinical and EKG findings. A correct interpretation of an EKG makes and accurate diagnosis in 75% of patients living with HF (sensitivity of 81%, specificity of 51%, positive predictive value of 59% and negative predictive value of 75%.[15] Another widely used study is chest radiography (X-rays), which remains as an important complementary diagnosis tool to exclude other relevant causes of dyspnea, such as pulmonary diseases that could give similar symptomatology of decompensating HF. It has been proposed that the echocardiogram is the best diagnostic tool since it allows the identification of cardiac dysfunction in an accurately and non-invasive way. Its main utility in a PC scenario is to confirm the diagnosis. The use of echocardiography in a PC scenario, should be part of the diagnostic tools available to all PC settings in patients with high suspicious

of HF. Finally, Natriuretic Peptides are useful in the diagnosis of established HFrEF, but their accessibility and distribution continue to be limited in PC scenarios in Mexico. As its circulating levels are closely related to eGFR, its interpretation requires consideration of this parameter.[16]

Other cardio-renal impairments related to HBP

Pathological mechanisms linked to the modulation of traditional risk factors and their future interrelation with cardiorenal impairments are heterogenous. It has been described that an increase in the hemodynamic load and pressure elevates the intra-abdominal venous resistance, which lead to a stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. This essential physiopathological mechanism are often combined with low-grade chronic inflammation, endothelial dysfunction, and a high production of reactive oxygen species, which induces fibrosis in the heart, kidney, and blood vessels. Thus, it is not surprising to see that several organs and systems are simultaneously affected. Overall, there are other several conditions related to HBP that go beyond the scope of this work. These patients are likely to have a high prevalence of diabetes, glucose intolerance, obesity, and dyslipidemia which also contribute to an unfavorable interaction for vascular damage and the development of ASCVD manifestations, such as atrial fibrillation, ischemic heart disease, peripheral artery disease, among others.

Take-home messages

HBP is one of the main risk factors for the development of ASCVD whose subclinical onset is documented in various studies. Kidney and heart damage are just two examples of the complex interplay of pathophysiological mechanisms that explain multi-organ damage in HBP. The search for a decrease in eGFR, albuminuria, LVH, and HF in patients living with HBP is mandatory in a PC setting, as the prompt and early identification of these conditions are the only way to reduce the long-term incidence of ASCVD in Mexican population.

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