Sensitivity and specificity of increased pulse pressure as a diagnostic test for K/DOQI stage III-b CKD

Ana I. Pérez-Castañeda,¹ Gilberto F. Vázquez-de Anda,^{1*} Patricia Cerecero-Aguirre,¹ Rodolfo Rivas-Ruiz,² María G. Delaye-Aguilar¹ and Juan O. Talavera²

¹Multidisciplinary Health Clinic, Universidad Autónoma del Estado de México, State of Mexico; ²Clinical Research Training Center, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City; ³Directorate of Teaching and Research, Centro Médico ABC, Mexico City. Mexico

Abstract

Background: Increased pulse pressure (IPP) is associated with an estimated glomerular filtration ≤ 60 mL/min/1.73 m²; thus, it can be useful as a diagnostic test to identify people with K/DOQI stage III-b chronic kidney disease (CKD). **Objective:** To determine the usefulness of IPP as a diagnostic test for K/DOQI stage III-b CKD. **Method:** Diagnostic test study that included adult patients without comorbidities, registered in the Health Workers Cohort. The CKD-EPI formula was used to calculate glomerular filtration. Pulse pressure was determined by subtracting diastolic from systolic blood pressure. Sensitivity, specificity, positive predictive value, negative predictive value and prevalence were calculated using standard formulas. A ROC curve was generated to determine the area under the curve. **Results:** A total of 6,215 patients were included. An IPP ≥ 50 mmHg was observed to have a sensitivity of 74 %, specificity of 70 %, positive predictive value of 1 %, negative predictive value of 100 % and a prevalence of 1 %. The inflection point in the ROC curve to identify K/DOQI III-b CKD was 0.71. **Conclusion:** An IPP ≥ 50 mmHg is useful as a diagnostic test to identify people with K/DOQI stage III-b CKD.

KEY WORDS: Pulse pressure. Diagnostic test. Glomerular filtration. K/DOQI III-b.

Sensibilidad y especificidad de la presión de pulso ampliada como prueba diagnóstica de IRC estadio K/DOQI III-b

Resumen

Introducción: La presión de pulso ampliada (PPA) se asocia a un filtrado glomerular calculado ≤ 60 mL/minuto/1.73 m², por lo que puede ser útil como prueba diagnóstica para identificar a personas con insuficiencia renal crónica (IRC) estadio K/DOQI III-b. **Objetivo:** Determinar la utilidad de la PPA como prueba diagnóstica de IRC estadio K/DOQI III-b. **Método:** Estudio de prueba diagnóstica que incluyó a pacientes adultos sin comorbilidades, registrados en la Cohorte de Trabajadores de la Salud. Se utilizó la fórmula CKD-EPI para calcular la filtración glomerular. Se determinó la presión de pulso restando la presión arterial diastólica a la presión arterial sistólica. Se calculó sensibilidad, especificidad, valor predictivo positivo, valor predictivo negativo y prevalencia. Se elaboró una curva ROC para determinar el área bajo la curva. **Resultados:** Se incluyeron 6215 pacientes. Se observó que una PPA ≥ 50 mm Hg tuvo sensibilidad de 74 %, especificidad de 70 %, valor predictivo positivo de 1 %, valor predictivo negativo de 100 % y prevalencia de 1 %. El punto de inflexión en la curva ROC para identificar IRC K/DOQI III-b fue de 0.71. **Conclusión:** La PPA ≥ 50 mm Hg es útil como prueba diagnóstica para identificar a personas con IRC estadio K/DOQI III-b.

PALABRAS CLAVE: Presión de pulso. Prueba diagnóstica. Filtración glomerular. K/DOQI III-b.

Correspondence:

*Gilberto F. Vázquez-de Anda
E-mail: gf_vazquez@hotmail.com

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Introduction

Chronic Kidney Disease (CKD) is a condition that at advanced stages increases the risk of cardiovascular disease-related death.¹⁻³ If detected at early stages, timely treatment can be started to preserve renal function and delay the start of replacement therapy with dialysis and/or hemodialysis, so far the only effective treatment for these patients.¹⁻⁵ Some patients may spend the first stages of the disease asymptomatically, and due to limited accessibility to health services,^{1,3} CKD is usually diagnosed at advanced stages, when late complications of the disease are present with replacement treatment indication, which increases the risk of death.^{1,6}

Recent studies have identified increased pulse pressure (IPP) as a predictor of organ damage and cardiovascular risk,⁶⁻⁸ and it is present in patients with CKD. An IPP ≥ 45 mmHg⁶ is associated with a decline in glomerular filtration (GF) regardless of age, gender, body mass index and presence of diabetes.^{7,8} However, Odaira et al.⁹ found no association between CKD and Doppler ultrasound pulse reflection wave, which casts doubt on the usefulness of pulse pressure as an indicator of glomerular filtration rate (GFR).⁹

Currently, the Kidney Disease Outcomes Quality Initiative (K/DOQI) scale,¹ which is based on GFR, is used to stage CKD. GFR can be estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which includes age, serum creatinine, gender and ethnicity. The scale identifies five CKD stages, with stage III-b (30 to 45 mL/min/1.73 m²) being associated with cardiovascular death. K/DOQI stage III-b can correspond to a target population in clinical practice to early identify patients with CKD. The association between IPP and decreased eGFR may have diagnostic value for this target population, and could early identify them in order for early treatment to be offered.

Therefore, and given the importance of developing new diagnostic screening methods that allow early identification of kidney disease, the purpose of our study was to determine the usefulness of IPP to identify patients with K/DOQI stage III-b CKD.

Method

This is a diagnostic test study.

For the selection and description of participants, the information obtained through a non-probabilistic

sample selected by convenience among adult subjects without comorbidities who participated in the Mexican study of the Health Workers Cohort was reviewed. This cohort is made up of employees and relatives of workers from the Mexican Institute of Social Security of the State of Morelos, the National Institute of Public Health and the Autonomous University of the State of Mexico. Prior to initiating the study, the corresponding protocol was reviewed and approved by the ethics and research committees of the participating institutions.

A total of 13,275 subjects were invited to participate in the Health Workers Cohort Study between March 2003 and April 2006. A registry was developed for the 10,192 subjects who participated. The information of 9,142 patients whose data for the performance of the study were complete was reviewed. Data from patients aged < 18 years and with conditions that alter pulse pressure, such as diabetes, hypertension and heart disease, among others, were excluded. Finally, the data of 6,215 adult subjects without comorbidities were analyzed (Fig. 1). Biochemical and anthropometric data from 6,215 adult subjects without comorbidities included in the Health Workers Cohort database were included.

Patient weight was determined using a calibrated electronic scale (BC-533 model, Tanita); the participants were weighed barefoot and with minimum clothing. Height was measured using a conventional stadiometer (Seca) with the patient standing barefoot, shoulders down, and with the head in position to maintain the Frankfurt plane. Measurements were taken with the tape in a horizontal plane, perpendicular to the vertical scale, touching the top of the head at the moment of inspiration.

Blood pressure was measured while the participants were sitting with the arm resting on a flat surface and at the level of the heart; a sphygmomanometer with a Citizen automatic digital monitor was used. Nurses trained to carry out the blood pressure measurement procedure performed three measurements on each individual. Through concordance correlation coefficients, the reproducibility of anthropometric and clinical measurements was evaluated, with a concordance of 0.83 to 0.90 being determined.

Twenty milliliters of blood were obtained by peripheral venipuncture, asking the subjects to show up with more than 8-hour fasting prior to sample taking. Subsequently, all samples were analyzed in the same laboratory using a Selectra XL Instrument® equipment (Randox Laboratories Ltd, Antrim, UK) and in

Figure 1. Criteria used for the selection of the study population sample.

accordance with the procedure established by the International Federation of Clinical Chemistry.

IPP was determined as the difference of systolic blood pressure minus diastolic blood pressure. Considering that 40 mmHg is a pulse pressure normal parameter, an increase of at least 5 mmHg was determined to be the criterion to define IPP. For the present study, three categories were analyzed:⁶⁻⁸

- An increase of 5 to 9 mmHg (≥ 45 to ≤ 49 mmHg).
- An increase of 10 to 14 mmHg (≥ 50 to ≤ 54 mmHg).
- An increase equal to or greater than 15 mmHg (≥ 55 mmHg).

Finally, the estimated glomerular filtration rate (eGFR) was determined using the equation formulated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),¹⁰ which is expressed in mL/min/1.73 m² and is adjusted for each individual by ethnicity (white, black or other), age, gender and serum creatinine levels. Finally, glomerular filtration rate was classified according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) international guidelines, with the data of patients with a glomerular filtration ≤ 60 mL/min/1.73m² being analyzed.^{2,11,12}

The Excel program, version 2010, and the SPSS 21 statistical program, version 21, were used for statistical analysis.

2 x 2 tables were generated to contrast patient eGFR and pulse pressure data. For the diagnostic test, sensitivity, specificity, positive predictive value

(PPV), negative predictive value (NPV), prevalence, diagnostic certainty and likelihood ratio of the test were determined using standard formulas.¹³⁻¹⁵

A Receiver Operating Characteristic (ROC) curve was generated to determine the optimal cutoff point for detecting GF decrease through pulse pressure increase.¹⁴

Bioethical considerations

Prior to the start of the Health Workers Cohort Study, the corresponding protocol was reviewed and approved by the ethics and research committees of the participating institutions: Mexican Institute of Social Security (12CEI 09 006 14), National Institute of Public Health (13CEI 17 007 36) and Autonomous University of the State of Mexico (1233008X0236). Written informed consent was obtained from all participants prior to study enrollment. Confidentiality of participants' biometric data was guaranteed through identification of each subject with a registration number and not by name.

The present study met the risk-free research criteria stipulated in article 24 of the World Medical Association Declaration of Helsinki, as well as the criterion stipulated by title two, chapter 1, article 17, section 1 of the General Statute of Health Regulations in Matters of Research for Health. As for ethical aspects of research on human subjects, retrospective documentary research techniques and methods were used, whereby no intentional intervention was performed (risk-free research); notwithstanding, an informed consent letter was obtained, which was signed by the participants when they joined the cohort, where they agreed to answer a questionnaire, provide blood samples, and be anthropometrically measured.

Results

Data from 6,215 adult patients without comorbidities included in the Health Workers Cohort were analyzed. Participants' mean age was 41.3 ± 13.6 years, systolic pressure was 115 ± 12.9 mmHg, diastolic pressure was 70.1 ± 10.1 mmHg, pulse pressure was 45.3 ± 9.8 mmHg, serum creatinine was 0.9 ± 0.15 mg/dL, and eGFR was 85.9 ± 20.3 mL/min/1.73 m².

Table 1 describes data on sensitivity, specificity, positive predictive value, negative predictive value, prevalence and diagnostic certainty for patients with a glomerular filtration ≤ 60 mL/min/1.73 m² (K/DOQI III) and IPP ≥ 45 mmHg. Table 2 shows the values of the diagnostic test calculated for IPP ≥ 45 and an

Table 1. Summary of statistical analyses for an IPP $\geq$ 45 mmHg with GF $\leq$ 60 mL/min/1.73m² (K/DOQI stage III)

	IPP $\geq$ 45 mmHg	IPP $\geq$ 50 mmHg	IPP $\geq$ 55 mmHg
Sensitivity (%)	65	48	31
Specificity (%)	50	71	85
Positive predictive value (%)	10	11	14
Negative predictive value (%)	94	95	94
Prevalence (%)	8	7	7
Diagnostic certainty (%)	52	69	82
Area under the curve	0.57	0.59	0.58
95 % CI	0.55-0.60	0.56-0.62	0.55-0.61

IPP = increased pulse pressure, GF = glomerular filtration, CI = confidence interval.

Table 2. Summary of statistical analyses for an IPP $\geq$ 45 mmHg with GF $\leq$ 45 mL/min/1.73m² (K/DOQI stage IIIb)

	IPP $\geq$ 45 mmHg	IPP $\geq$ 50 mmHg	IPP $\geq$ 55 mmHg
Sensitivity (%)	85	74	47
Specificity (%)	49	70	84
Positive predictive value (%)	1	1	2
Negative predictive value (%)	100	100	100
Prevalence (%)	1	1	1
Diagnostic certainty (%)	50	70	84
Area under the curve	0.67	0.71	0.65
95 % CI	0.59-0.75	0.63-0.80	0.55-0.76

IPP = increased pulse pressure, GF = glomerular filtration, CI = confidence interval.

eGFR $\leq$ 45 mL/min/1.73 m², corresponding to K/DOQI stage III-b CKD.

The area under the curve reflected in the tables and the cutoff points for the tests were determined by generating ROC curves. Figure 1 shows the discrimination line of the test according to pulse pressure cross values $\geq$ 50 mmHg and eGFR $\geq$ 30 and $\leq$ 45 mL/min/1.73 m² (K/DOQI stage III-b).

Discussion

Our study demonstrates that a pulse pressure $\geq$ 50 mmHg has an acceptable diagnostic capacity to identify patients, without associated morbidities, with CKD at K/DOQI stage III-b. According to the Mexican Institute of Social Security, CKD at advanced stages of the disease is among the first 10 causes of general mortality and represents the eighth cause of death in males

at productive age and the sixth in women aged 20 to 59 years.^{3,4} Due to the above, it is urgent to early identify patients at risk of experiencing a decrease in glomerular filtration at stages where the disease is asymptomatic.

In our study, mean pulse pressure of the study population was observed to be 5 mmHg above the reference values (40 mmHg). According to the literature, this pulse pressure elevation is a factor for initiation and progression to K/DOQI stage III in the long term,⁶⁻⁸ given that, as pulse pressure increases, the rate of kidney disease progression grows.¹¹

Study subjects' age was not a risk factor for CKD; however, since glomerular filtration decreases by 1 mL/min/year from age 30 onwards, monitoring renal function at least once a year is recommended in adult patients. Currently, serum creatinine value or GFR calculation using standard formulas are regarded as screening tests.^{4,11}

Our study shows (through the ROC curve) that the test is able to identify two-thirds of patients with IPP ≥ 50 mmHg and a decrease in eGFR equivalent to K/DOQI stage III-b CKD.^{2,6-8,10-12,14}

The capability of pulse pressure to rule out a decrease in eGFR equivalent to K/DOQI stage III-b CKD (NPV) when the patient has a pulse pressure ≤ 50 mmHg is high.^{12,13,15} Calculation of predictive values to determine the probability of developing kidney disease depends on the prevalence in the study population; for this reason, PPV is low because the prevalence of the disease in our population is low, whereas NPV increases.^{12,13,15}

Our study determined that both prevalence and positive predictive value (PPV) were low; therefore, the test would detect K/DOQI stage III-b CKD in one out of every 100 patients using a rapid, non-invasive technique that is carried out at each visit to the doctor or health institution.^{12,13,15} Given that the obtained NPV is high, the test is able to rule out the disease in a patient with suspected K/DOQI stage III-b CKD.

On the other hand, we know that 70 % of the times that the test is performed in an individual the diagnosis will be correct, and that if the patient has an IPP ≥ 50 mmHg, his GF will be lower in comparison with healthy individuals; therefore, an IPP ≥ 50 mmHg can be used as a screening diagnostic test for K/DOQI stage III-b CKD.¹²⁻¹⁵

By itself, IPP is a characteristic that is present in patients with K/DOQ stage III-b CKD, is a predictor of organ damage and a cardiovascular risk factor.^{6,8} The particularity of IPP is its association with cardiovascular disease complications and death.¹⁶⁻¹⁸ Despite the evidence, Mari Odaira et al.⁹ and Colin D. Chue et al.¹⁹ claim that, although IPP can be present in patients with GF < 60 mL/min/1.73 m², in linear regression models adjusted for age, gender and some comorbidities, no association was observed between IPP and GF decline, and IPP could therefore not be used as a GF indicator.^{9,19} However, a PP increase ≥ 5 mmHg above normal values⁶ is associated with CKD due to the decrease in eGFR. Consequently, IPP can be used as a clinical marker to identify patients with CKD according to the K/DOQI guidelines.¹

Renal replacement therapy has an elevated cost that cannot be afforded by the patient in case of not having access to social security, and familial economic situation and patient quality of life are therefore severely affected when CKD occurs.^{1,3} Hence the importance of timely detection of GF decrease by means of new sensitive, specific, low-cost and easy-to-implement

diagnostic screening tests such as IPP, given that, at advanced stages of the disease (K/DOQI stages IV-V), the probability for the patient to suffer complications secondary to the disease itself or to late replacement therapy increases.^{1,3,8}

According to the results obtained, carrying out new studies is planned, which should include patients with comorbidities in order to determine new cutoff points, as well as the most recent data from patients of the Health Workers Cohort.

When analyzing the data, some limitations were identified: we had to exclude 2,927 individuals because the information was not complete. The main limitation of the study was that only data of people living in the States of Mexico and Morelos were included, and thus, the results cannot be generalized to the rest of the Mexican population.

Finally, our study demonstrates that patients who had an IPP ≥ 50 mmHg, had a GF ≤ 45 mL/min/1.73 m²; therefore, an IPP ≥ 50 mmHg can be used as a timely, sensitive and specific diagnostic screening test for K/DOQI stage III-b CKD.

Conclusion

An IPP ≥ 50 mmHg can be used as a sensitive and specific diagnostic screening test for K/DOQI stage III-b CKD early detection in adults without comorbidities.

Conflict of interests

None.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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