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It is time to adapt the definition of chronic kidney disease according to age

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Abstract

Chronic kidney disease is a condition with high morbidity, mortality and healthcare costs which affects all population groups, having a significant impact on their quality of life. Its classification has been modified over time and there is still no universal consensus to differentiate a physiological change in kidney clearance from a pathological change. Below, we will discuss the importance of reconsidering the definition and classification in the general population according to age, including children and adults. (*Acta Med Colomb* 2021; 46. DOI: <https://doi.org/10.36104/amc.2021.2080>).

Keywords: *chronic renal insufficiency, chronic renal failure, classification, aging.*

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In medicine, the definitions and classifications of the various diseases should be uniform throughout the world, so healthcare workers speak the same language, promoting the timely detection of health problems, impacting treatment and promoting research. This article analyzes the importance of reformulating the definition and classification of chronic kidney disease (CKD) in the general population according to age, including children and adults.

Chronic kidney disease is a public health problem with high morbidity and mortality and elevated costs for healthcare systems around the world. It affects both adults and children, with a negative impact on the individual and family quality of life of those who have it. Chronic kidney disease is a functional, structural or histological kidney disorder lasting three or more months, and affecting the patient's health. To have CKD, the glomerular filtration rate (GFR) calculated by validated formulas or estimated, must be persistently less than 60 ml/min/1.73m² (for at least three months), which is enough to classify the patient as having this disease. If the GFR is equal to or greater than 60 ml/min/1.73m², other criteria must be met to diagnose this disease, such as: evidence of an irreversible functional disorder of one of the kidney functions such as abnormal albumin excretion, urinary sediment changes (proteinuria or hematuria in two out of three samples), acid-base balance control, electrolytes, total body water, or blood pressure; structural abnormalities such as kidney malformations, pathological cysts, tumors, or kidney stones; and/or irreversible histological changes on kidney biopsy (1).

A timely diagnosis of this entity requires a focus on the

entire medical chart, identifying risk factors, an adequate medical history, a targeted physical exam and diagnostic tools for detecting these abnormalities, such as measurement of creatinine, cystatin C, urea nitrogen, electrolytes; urinalysis, albuminuria; urinary tract ultrasound, kidney scan, urinary tract tomography and/or renal biopsy, according to the clinical context. However, as screening strategies in the at-risk population (identified through an appropriate clinical history), a urinalysis, albuminuria and serum creatinine are sufficient for detecting most cases.

As CKD progresses, complications develop such as HTN, anemia, mineral bone disease, malnutrition, and electrolyte and acid-base disorders, with high morbidity and mortality. When stage 5 is reached, renal replacement therapy should be considered, such as hemodialysis, peritoneal dialysis or transplant, and, in selected cases, conservative management, all of which have quality of life and healthcare system cost implications (1).

The main etiologies of CKD worldwide are diabetes mellitus (DM), arterial hypertension (HTN) (2), the use of nephrotoxic medications or substances, primary glomerulopathies, autoimmune diseases like systemic lupus erythematosus (SLE), childhood urinary tract infections, hereditary kidney diseases, congenital anomalies of the kidney and urinary tract (CAKUT) (3, 4), etc. Diabetes mellitus and HTN explain approximately 80% of cases, which is vitally important because they are very prevalent diseases with public health significance due to their high morbidity and mortality, as they are the main cause of death worldwide since they foster cardiovascular problems, and they are

preventable and treatable. On the other hand, in children, urinary tract infections and CAKUTs are the main causes of CKD, which, if identified promptly, may favorably impact the prognosis (2-4).

In economic terms, CKD is considered a high-cost disease which generates direct and indirect costs to the healthcare system in Colombia, representing approximately 2-4% of the nation's healthcare budget. In 2019, there were an estimated 1,406,364 people diagnosed with CKD, regardless of the GFR level, with higher charges for stages 4 and 5, in which the complications increase and quality of life deteriorates, not counting the healthy and productive years of life lost by people due to this disease and the high probability of dying, in many cases at a young age, due to the greater prevalence of cardiovascular disease in this group and associated comorbidities such as diabetes and hypertension (5).

Towards the end of the 90s, the definition of CKD was unified, and a universal classification was established, promoted by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI). This has allowed this disease to be studied and terms to be standardized to speak a common language (1, 5). The definition and classification have been modified over time and have been adopted by many countries around the world, including Colombia.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD and the Latin American CKD guidelines from that same year classify the disease in five stages, depending on the glomerular filtration rate, adding the degree of albuminuria to each category; this classification is the same for all age groups (from children to the elderly) and globally applied. Thus, according to the current classification, stage G1 has a $\text{GFR} \geq 90 \text{ ml/min/1.73m}^2$; G2 between 60 and 89 ml/min/1.73m^2 ; G3 between 30 and 59 ml/min/1.73m^2 , subdivided into G3a if the GFR is between 45 and 59 ml/min/1.73m^2 and G3b if it is between 30 and 44 ml/min/1.73m^2 BSA; G4 between 15 and 29 ml/min/1.73m^2 ; and G5 less than 15 ml/min/1.73m^2 . According to albuminuria (measured in urine as the ratio of albuminuria to gram of creatinuria), category A1 has albuminuria less than 30 mg/g (known as normal or slightly increased albuminuria); A2 between 30 and 300 mg/g (moderate albuminuria, previously known as microalbuminuria) and A3 greater than 300 mg/g (severely increased albuminuria). Lower GFRs and higher albuminuria lead to much greater disease progression, associated complications and mortality (1, 6).

Based on this definition and classification, the global prevalence of CKD ranges from 9 to 13%, and may even reach 20% in patients over the age of 60, as reported cases vary according to the GFR measured, early diagnosis, related chronic diseases and their recording; with better detection in developed countries (7, 8). In Colombia, according to the high-cost bill for 2019, CKD affected 1.8% of the population, which indicates under-reporting when compared to the statistics from other countries, in addition to late detection of

CKD, in which up to 50% of the cases which reach stage 5 are classified as having an idiopathic or unknown cause (9).

The biggest problem with this classification is that it overestimates the prevalence of CKD in the elderly and underestimates the problem in children and young people, since it does not discriminate according to age group. Given the physiological aging of the kidneys, there should clearly be a differentiation by patient age (10, 11). A person is born with immature kidneys and glomerular filtration ranging from 30 to 40 ml/min/1.73m^2 , reaching optimal maturation at age one, with a glomerular filtration rate ranging from 90 to 120 ml/min/1.73m^2 which is maintained until young adulthood (12). After age 40, physiologically, 0.5 to 1 ml/min is lost per year, unrelated to any kidney disease (10,11). Two examples are given to better illustrate this:

A 90-year-old asymptomatic white woman with no other comorbidities had a creatinine of 1.0 mg/dl, a BIS-1 calculated GFR of 43 ml/min/1.73m^2 (13), and normal urine cytochemistry. She was sent to nephrology for stage 3b A1 CKD, due to a high risk of complications, disease progression, need for dialysis and greater mortality. If the current 2012 KDIGO classification (1) is used, the referring physician is right, and this patient was properly classified. If this simple cut-off point and same approach are used for 100 elderly people of the same age, who are otherwise healthy, they will all be classified the same. However, if you take into account that the expected GFR for this age is 40 ml/min/1.73m^2 (using the Keller formula), which is in line with the calculated GFR (14), and that this patient is asymptomatic and has a normal urinalysis, the patient really does not have a kidney problem affecting her health; what she has is the expected kidney aging for her age, which is completely physiological.

The foregoing is a big public health problem because CKD is overdiagnosed in the elderly population with the psychological and social implications of stigmatizing a person with this type of disease, in addition to the high cost for the healthcare system and the implications of saturating the referral system, thus reducing the possibility of offering care to other patients who really are affected by this condition. This is why it is important to have an appropriate definition, in order to reduce the healthcare resources used to provide care for a physiological condition of kidney aging without a real, identified renal disease. It should be clarified that multiple comorbidities are common in the elderly, and that many elderly persons may ultimately have CKD; thus, a timely and comprehensive assessment must be performed to determine the presence of structural, biochemical and/or renal function disorders. However, the current definition limits appropriate classification because it does not take physiological kidney aging into account.

On the other hand, the following case presents a 30-year-old woman with no known comorbidities who, during a personalized medical check-up was found to have a creatinine level of 1.1 mg/dl with a CKD-EPI estimated GFR of 67.3

ml/min/1.73 m², verified by a 24-hour urine measurement and a renal scan. She had a normal blood pressure and a normal physical exam, with no albuminuria and no abnormalities in urine cytochemistry and ultrasound. According to the KDIGO CKD classification, this patient does not have CKD, since her GFR is greater than 60 ml/min/1.73 m² and she has no markers of kidney disease. However, her GFR is clearly much less than expected for her age (100 ml/min/1.73 m² by the Keller formula) (14), although the available evidence is not clear regarding the long-term progression of these patients, and whether they merit a specialized assessment, follow up and renal protection measures geared towards lifestyle changes and avoiding exposure to nephrotoxic agents.

Therefore, some global authorities on this subject propose CKD detection likewise based on GFR, but taking into account the patient's age. Thus, for example, for children and young adults (<40 years), the proposal is to raise the limit for detection to a GFR of 75 ml/min/1.73 m² (currently 60), continue with a GFR limit of 60 ml/min/1.73 m² for 40 to 64-year-old patients, and lower the GFR limit in those over 65 to a GFR of 45 ml/min, in light of the lack of a clear, significant difference in mortality compared with a 60 ml/min/1.73 m² cutoff in elderly patients (15).

That said, in the case of a patient with CKD defined according to functional, biochemical, anatomical or histological criteria, the current classification by GFR in five stages would be maintained. Likewise, there would be no changes in the albuminuria categories, as well as in other kidney damage markers (proteinuria, glomerular hematuria, structural or histological abnormalities). This would avoid overdiagnosing the elderly and subdiagnosing young people, keeping in mind the relationship between mortality and GFR (16), with the limitation entailed in modifying a classification which has already been standardized worldwide, and the discrimination by groups which could make it more difficult to apply, since physicians who are not specialists in the subject might not remember it.

Finally, it is clear that kidney aging is an age-related condition in which the GFR reduction is physiological and unrelated to underlying diseases (16), with early detection and prompt comprehensive treatment of cardiovascular risk and comorbidities having a great impact. Therefore, it is time to determine if modifying the current definition to an age-adapted one produces a significant change in healthcare costs, affects patient follow up, and makes a difference in mortality and complications related to the progression of kidney disease. There are different positions regarding the correct definition; however, a consensus must be reached on this in order to reach the definition which best fits the prognosis and clear up the questions regarding age.

In conclusion, we underscore that the definition of CKD is unified globally with objective criteria, which has made

it easier to study in all countries, with the limiting factor that there is no distinction by age groups and physiological kidney aging is not taken into account.

This article calls for a universally applied adaptation of the CKD definition according to age, considering the impact on patients' morbidity, mortality and quality of life, and seeking strategies to optimize the healthcare resources allocated to caring for this very prevalent and costly disease.

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