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Chronic kidney disease of nontraditional etiology in Central America: a provisional epidemiologic case definition for surveillance and epidemiologic studies

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SYNOPSIS

Over the last two decades, experts have reported a rising number of deaths caused by chronic kidney disease (CKD) along the Pacific coast of Central America, from southern Mexico to Costa Rica. However, this specific disease is not associated with traditional causes of CKD, such as aging, diabetes, or hypertension. Rather, this disease is a chronic interstitial nephritis termed chronic kidney disease of nontraditional etiology (CKDnT). According to the Pan American Health Organization (PAHO) mortality database, there are elevated rates of deaths related to kidney disease in many of these countries, with the highest rates being reported in El Salvador and Nicaragua. This condition has been identified in certain agricultural communities, predominantly among male farmworkers. Since CKD surveillance systems in Central America are under development or nonexistent, experts and governmental bodies have recommended creating standardized case definitions for surveillance purposes to monitor and characterize this epidemiological situation. A group of experts from Central American ministries of health, the U.S. Centers for Disease Control and Prevention (CDC), and PAHO held a workshop in Guatemala to discuss CKDnT epidemiologic case definitions. In this paper, we propose that CKD in general be identified by the standard definition internationally accepted and that a suspect case of CKDnT be defined as a person age < 60 years with CKD, without type 1 diabetes mellitus, hypertensive diseases, and other well-known causes of CKD. A probable case of CKDnT is defined as a suspect case with the same findings confirmed three or more months later.

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SYNOPSIS

En los dos últimos decenios, los expertos han notificado un aumento del número de defunciones causadas por enfermedad renal crónica (ERC) a lo largo de la costa del Pacífico de Centroamérica, desde el sur de México hasta Costa Rica. Sin embargo, esta enfermedad específica no está asociada con las causas tradicionales de ERC, como envejecimiento, diabetes o hipertensión. En cambio, esta enfermedad es una nefritis intersticial crónica denominada enfermedad renal crónica de causas no tradicionales (ERCnT). Según la base de datos de mortalidad de la Organización Panamericana de la Salud (OPS), se registran tasas de mortalidad elevadas relacionadas con la enfermedad renal en muchos de estos países; las más elevadas se informaron en El Salvador y Nicaragua. Esta enfermedad ha sido identificada en algunas comunidades agrícolas, predominantemente en trabajadores agrícolas varones. Como los sistemas de vigilancia de la ERC en Centroamérica están en desarrollo o son inexistentes, los expertos y los organismos gubernamentales han recomendado elaborar definiciones de caso estandarizadas con fines de vigilancia, para monitorear y caracterizar esta situación epidemiológica. Un grupo de expertos de los ministerios de salud centroamericanos, los Centros para el Control y la Prevención de Enfermedades de los Estados Unidos (CDC) y la OPS se reunieron en un taller realizado en Guatemala para debatir posibles definiciones de caso epidemiológicas de ERCnT. En este artículo proponemos que, en general, la ERC se identifique mediante la definición normalizada internacionalmente aceptada y que un caso presunto de ERCnT se defina como: persona menor de 60 años con ERC, sin diabetes mellitus de tipo I, enfermedades hipertensivas ni otras causas conocidas de ERC; y un caso probable de ERCnT se defina como un caso presunto con los mismos resultados confirmados tres meses después o más.

Keywords

Renal insufficiency; chronic; kidney diseases; nephritis; chronic disease; epidemiological surveillance; diagnosis; differential; Central America

Palabras clave:

Insuficiencia renal crónica; enfermedades renales; nefritis; enfermedad crónica; vigilancia epidemiológica; diagnóstico diferencial; América Central

INTRODUCTION

Chronic kidney disease (CKD) is a condition that affects populations of developed and developing countries alike. In most parts of the world, CKD is associated with older age and such chronic conditions as diabetes (regardless of the type), hypertension, and cardiovascular disease (1). However, along the Pacific coast of Mesoamerica from southern Mexico to Costa Rica (especially in El Salvador and Nicaragua), high prevalence of CKD not associated with the most commonly reported etiologies worldwide has been identified in certain agricultural communities, predominantly among male farmworkers (2–4). Experts have estimated that this disease has caused premature deaths of at least 20 000 men (5).

National CKD mortality rates among males show excess mortality in Nicaragua and El Salvador (66 and 64 per 100 000, respectively), compared to Guatemala (16 per 100 000), Panama (15 per 100 000), Costa Rica (8 per 100 000), and the United States of America (4 per 100 000) (6). In addition, CKD mortality rates are higher among men than among women (e.g., in Nicaragua, 66 vs. 21 per 100 000, respectively). CKD prevalence rates as high as 28% in men and 14% in women have been found in high-risk agricultural communities in El Salvador, and prevalence of reduced kidney function was estimated at 20% in men and 8% in women in high-risk areas of Nicaragua (7, 8).

For the purposes of this article, we will use the term chronic kidney disease of nontraditional etiology (CKDnT) to describe the characteristics of this form of CKD identified in the Pacific coast of Mesoamerica, recognizing that this type of CKD is not associated with commonly known causes, such as diabetes and hypertension (Figure 1). In Figure 1, the top circle represents all CKD. Parts of the CKD circle overlapping with the diabetes or hypertension circles represent CKD with traditional causes, and the remaining red part of this circle represents CKDnT. The small white circle represents other known causes of CKD, including congenital malformations, polycystic kidney disease, sickle cell disease, lupus, vasculitis, myeloma, and others; it overlaps with diabetes and hypertension. (Note that the amount of overlap of circles in the diagram is not proportional to disease prevalence in actual populations.)

CKDnT is also referred to as Mesoamerican nephropathy (MeN) in other publications (2, 4, 9). Several public health authorities have declared an epidemic of CKD in this region, urging rapid and coordinated efforts to address the problem (3, 10, 11).

Clinical characteristics

CKDnT is a condition characterized as silent in initial stages and that often has rapid progression to end-stage renal disease (ESRD), though the time frame is not well known. CKDnT is mainly a tubulointerstitial disease with tubular atrophy, interstitial fibrosis, and glomerulosclerosis (12, 13). Clinical descriptions of CKDnT indicate that proteinuria and hypertension are uncommon. However, elevated uric acid and electrolyte imbalances are common, particularly low potassium (12, 14, 15).

A laboratory assessment is required to identify CKDnT in the early stages of disease. Serum creatinine levels are measured and used to calculate the reduced kidney function, most often expressed as estimated glomerular filtration rate (eGFR). Some cases of CKDnT have been observed to progress to ESRD in a few years after the first evidence of reduced kidney function (16), which is quicker than typical CKD progression. Ultimately, when kidney failure occurs in advanced stages of CKDnT, resource-intensive renal replacement therapies (dialysis and kidney transplant) are necessary to sustain life. Because we do not know the etiology of CKDnT, effective medical, environmental, and behavioral interventions to slow its progress are not well understood.

Epidemiology

In Central America, some studies have estimated the prevalence of CKDnT in selected populations, but using slightly different definitions of CKD. Some use only eGFR to define

CKDnT, while others use absolute serum creatinine level. In addition, many studies only use one test (e.g., eGFR or absolute serum creatinine) even though CKD needs to be confirmed with a second test at least three months later (17–19). Furthermore, there are several equations for calculating eGFR from serum creatinine levels, making direct comparisons of prevalence rates across studies difficult. For instance, a prevalence study in the northwestern region of Nicaragua defined a CKD case as a person with an eGFR < 60 mL/min/1.73m^2 (19). Meanwhile, a study from coastal El Salvador defined chronic renal failure as a person with a serum creatinine level ≥ 1.5 mg/dL (17).

Lack of association between CKD and traditional causes (i.e., diabetes and hypertension) is frequently reported in recent Central American studies. Of the 98 cases of CKD identified in a study in rural areas of Nicaragua, 92% did not have diabetes and 64% did not have a history of hypertension, indicating that, by exclusion, 57%–64% of the participants had CKDnT (7). Among the 139 persons with CKD in a population-based study in a coastal region of El Salvador, 86% did not have diabetes and 55% did not have diabetes or hypertension (14). In another study carried out in coastal El Salvador, among 37 people diagnosed with chronic renal failure, 38% had diabetes or hypertension, and the remaining 62% had no known etiology (17).

CKD mortality rates differ throughout Central America. The mortality rate (per 100 000 population) for all types of CKD among males increased from 42.2 to 64.5 in El Salvador and 47.7 to 66.7 in Nicaragua between 2000 and 2009 (6). In 2009, the CKD mortality rates among males in El Salvador and Nicaragua were more than four times the rate of the next highest country in the region: Panama (15 per 100 000 population). El Salvador and Nicaragua are among the 10 countries with the highest mortality rates for renal disease worldwide (9). According to the El Salvador Ministry of Health, CKD is the second leading cause of death in males of working age in the country. In Nicaragua, mortality rates per 100 000 population for chronic renal insufficiency in 2005 varied among the departments (20). The departments of León and Chinandega had the highest mortality rates among males (60 per 100 000 population). The department with the next highest rate among males was Granada (20 per 100 000), while the national rate was 13 per 100 000 (20). Several Central American mortality and prevalence studies have shown that CKD rates are higher among men than among women, but rates among women are also elevated compared to the United States (3, 7–9, 14, 15, 20–22).

Currently, CKD surveillance systems in Central America are under development or are nonexistent. This makes it difficult to determine what the most common etiologies are, to estimate the true burden of this condition, and to determine the proportion of persons with CKD who could be classified as CKDnT (3). Several experts and governmental bodies have recommended strengthening surveillance systems capable of monitoring CKD incidence and prevalence at the population level (5, 9, 11, 23). Implementing CKD surveillance systems throughout Central America is essential to advancing knowledge about CKDnT. Experts stressed the importance of creating a standardized case definition for CKDnT both in 2012 at the First International Research Workshop on Mesoamerican Nephropathy and in 2013 at the 52nd Directing Council meeting of the Pan America Health Organization (PAHO) (9, 23).

In response to this situation, a group of surveillance experts, subject matter experts in vital records, epidemiologists, and nephrologists from Central America carried out an inclusive process to propose a standardized epidemiologic case definition for CKDnT.

METHODS

The Council of Ministries of Health of Central America and the Dominican Republic (COMISCA), PAHO, and the U.S. Centers for Disease Control and Prevention (CDC) coordinated a collaborative process to develop or strengthen CKD surveillance and to draft appropriate data collection tools and methods in response to the COMISCA Resolution from its XXXV meeting in 2011 (24) and the PAHO Resolution CD52.R10 on chronic kidney disease in agricultural communities in Central America from 2013 (23). Subject matter experts in three fields key for assembling a CKD surveillance system (surveillance, vital records, and nephrology) were invited from eight countries: Belize, Costa Rica, the Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, and Panama. Subject matter experts on surveillance and vital records were appointed by the ministry of health of each country. Nephrologists were designated by the national chapter of each country of the Latin American Society of Nephrology and Hypertension (SLANH). A total of 28 persons from the eight countries participated: 11 nephrologists, 11 subject matter experts in surveillance, and 6 subject matter experts in vital records. There was representation from each country, but there was not a representative from each subject matter from each country. An additional 6 persons from three international public health agencies (CDC, PAHO, and COMISCA) also participated.

The Epidemiologic Workgroup, comprised of experts from COMISCA and the ministries of health of five countries, was charged with drafting suspect and probable CKDnT epidemiologic case definitions, with the support of representatives from CDC, PAHO, and COMISCA. Once delegates from all participating countries were appointed to their respective workgroups, the Epidemiologic Workgroup initiated remote consultations, following the Delphi technique. After making the initial consultation, the Epidemiologic Workgroup produced a draft document that included the opinions of experts and concepts that emerged from a literature review. The expert consultation was repeated in two additional cycles.

On 16 and 17 December 2013, the Epidemiologic, Vital Records, and Clinical Case Definitions Workgroups (comprised of 34 people) convened an in-person workshop in Guatemala City to discuss and further develop the case definitions. The discussion considered both the epidemiologic and operational aspects of the case definitions, and input was provided from all workgroups to obtain the final version of the case definition presented here.

Case definitions

We propose using the widely accepted definition of CKD and staging of the disease as a starting point for the suspect and probable epidemiologic case definitions of CKDnT. By using the widely accepted CKD case definition, we encourage epidemiologic studies and

surveillance to capture all CKD cases, and then further characterize the proportion of CKD attributable to traditional and nontraditional causes.

Chronic kidney disease case definition.—We refer to the CKD case definition established by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (Figure 2) (18). This chronic kidney disease case definition categorizes CKD into five stages (G1–G5) and two substages (G3a and G3b) based on eGFR, which can be seen in the rows of Figure 2. In addition, albuminuria categories (columns A1–A3 in Figure 2) are combined with eGFR to create risk profiles (low risk to high risk) and are indicated by colorfilled cells in Figure 2. As eGFR decreases and albuminuria increases, risk increases.

The KDIGO criteria for CKD requires one or more markers of kidney damage or a decreased eGFR present for > 3 months) (18). Markers of kidney damage include the following: albuminuria (albumin creatinine ratio (ACR) ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥ 3 mg/mmol]); urine sediment abnormalities; electrolyte and other abnormalities due to tubular disorders; abnormalities detected by histology; structural abnormalities detected by imaging; and history of kidney transplantation. Decreased eGFR is defined as an eGFR < 60 ml/min/1.73 m^2 (categories G3a-G5).

The use of this standard chronic kidney disease definition will allow Central American countries to compare both CKD-related and CKDnT-related incidence and prevalence regionally as well as worldwide.

Suspect case of chronic kidney disease of nontraditional etiology.—A suspect case of CKDnT is a person with one abnormal result that meets the KDIGO CKD criteria ***AND*** who meets all of the following criteria:

1. no history of type 1 diabetes mellitus
2. no history of hypertensive diseases (hypertensive heart disease, hypertensive chronic kidney disease, hypertensive heart and chronic kidney disease, secondary hypertension)
3. no history of other known cause(s) of CKD (e.g., congenital malformations, polycystic kidney disease, sickle cell disease, lupus, vasculitis, myeloma, and others)
4. age < 60 years

Probable case of chronic kidney disease of nontraditional etiology.—A probable case of CKDnT is a suspect case with a *second* abnormal result, obtained at least three months after the first result, that meets the widely accepted criteria of CKD (see above).

DISCUSSION

We propose epidemiologic case definitions for suspect and probable CKDnT. These case definitions are for epidemiologic studies and surveillance. The case definitions are not intended for surveillance of CKDnT in renal replacement therapy centers, where a clinical case definition is most appropriate. Nor are the case definitions intended for surveillance

of CKDnT through vital records, where a case identification approach based on ICD-10 is appropriate. The proposed clinical case definition for CKDnT is described in an article elsewhere in this issue of this journal (25).

These CKDnT case definitions are not intended to be used to create stand-alone CKDnT surveillance systems. Rather, we envision Central American countries establishing CKD surveillance systems that would either capture or permit an estimation of all CKD cases from all regions of the country. Then, they can apply these CKDnT case definitions to characterize persons with CKD by cause. Capturing all CKD cases is useful to ministries of health for planning purposes to meet the needs for renal replacement therapy of all those who require it.

Long-standing diabetes mellitus and hypertension are the two major causes for CKD worldwide (26). We acknowledge that the widely accepted CKD case definition was derived from populations that had higher prevalence of diabetes mellitus–associated CKD and hypertension-associated CKD than what has been observed in Central America. Therefore, it is important that this proposed case definition be validated in Central American populations. Acknowledging accepted practice, we propose the established cutoff for albuminuria (an ACR ≥30 mg/g). However, we do not recommend using dipstick proteinuria as a screening tool for case finding because clinical observations and epidemiological findings indicate that persons with CKDnT can have decreased eGFR without signs of proteinuria (9, 14).

Several studies in Central America have characterized CKD patients as with or without history of diabetes mellitus or hypertension (7, 14, 17). For this reason, a medical history without type 1 diabetes mellitus, hypertensive diseases (hypertensive heart disease, hypertensive chronic kidney disease, hypertensive heart and chronic kidney disease, and secondary hypertension) (27), or other known causes of CKD are the primary criteria for the CKDnT case definition. We include children in the CKDnT case definitions so that cases may be identified in the early stages of disease, allowing researchers to explore development and progression of CKDnT. Due to the inverse association between age and eGFR, and the use of eGFR as the primary diagnosis for CKDnT, we exclude persons aged ≥ 60 years from the CKDnT case definition. However, it is important that CKD surveillance, registries, and epidemiologic studies include persons ≥ 60 years old to assess disease trends in all age groups. This will allow ministries of health to assess the need for CKD treatment and for researchers to explore CKD progression in persons ≥ 60 years old.

These case definitions intend to set basic methodological recommendations to harmonize the epidemiological surveillance of CKDnT, which clearly represents an added value for all countries. However, adoption or adaptation of some specific definition is an issue of balance. For instance, inclusion or exclusion of children in the surveillance system might require some ethical considerations based on country-specific standards. In the same way, the upper age exclusion will limit the view of CKDnT in older people. Hence, the ministries of health in Central America have the flexibility to implement these case definitions as they see fit within the context of each country, taking into account the potential benefits or limitations derived from such decisions.

There are several methods for calculating eGFR. The Modification of Diet in Renal Disease (MDRD) equation is most often used for surveillance and epidemiological studies, while the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is used often in clinical settings (28). Both MDRD and CDK-EPI include adjustments for age, sex, and race/ethnicity. However, neither the MDRD nor CKD-EPI equations have been validated in Central American populations. It is critical that primary data points, including sex, age, weight, creatinine, albuminuria, and others, are collected and reported during CKD surveillance and epidemiologic studies. This will allow multiple equations for calculating eGFR to be applied to and validated in Central American populations. Since CKDnT is primarily a tubulointerstitial process, the frequency of albuminuria reported among persons with CKDnT is lower than that among persons with CKD associated with diabetes or hypertension or both. However, the appropriate albuminuria cutoff to discriminate the CKDnT cases is undefined. Therefore, we recommend collecting primary data on albuminuria in Central American populations.

The epidemiologic case definitions proposed here are for use with surveillance or epidemiologic studies. In addition to the clinical data and information needed to determine if a person has CKDnT, it is important to characterize individual- and population-level exposures in order to further the understanding of potential causes of CKDnT. Surveillance systems may only be able to capture essential data that are not too burden-some, while epidemiological studies and registries can collect more comprehensive data. Among exposures important to gather are: place of residence (farming community), occupational history (including agriculture, industry/sector, job duties, duration, workload, heat stress, and dehydration), pesticides, metals, infectious agents, and use of nephrotoxic medications.

It is important to establish an agreed-upon case definition for CKDnT as surveillance systems and registries are developed and further epidemiologic investigations are carried out in Central American countries. Adopting a standardized case definition will allow for findings across Central America to be compiled and compared, as well as measured against prevalence rates from other regions of the world. Because there are key scientific uncertainties surrounding CKDnT (e.g., etiology, pathogenesis, and effective interventions to improve health outcomes), this case definition is subject to change and will require validation in future studies and also use of data from existing prevalence studies.

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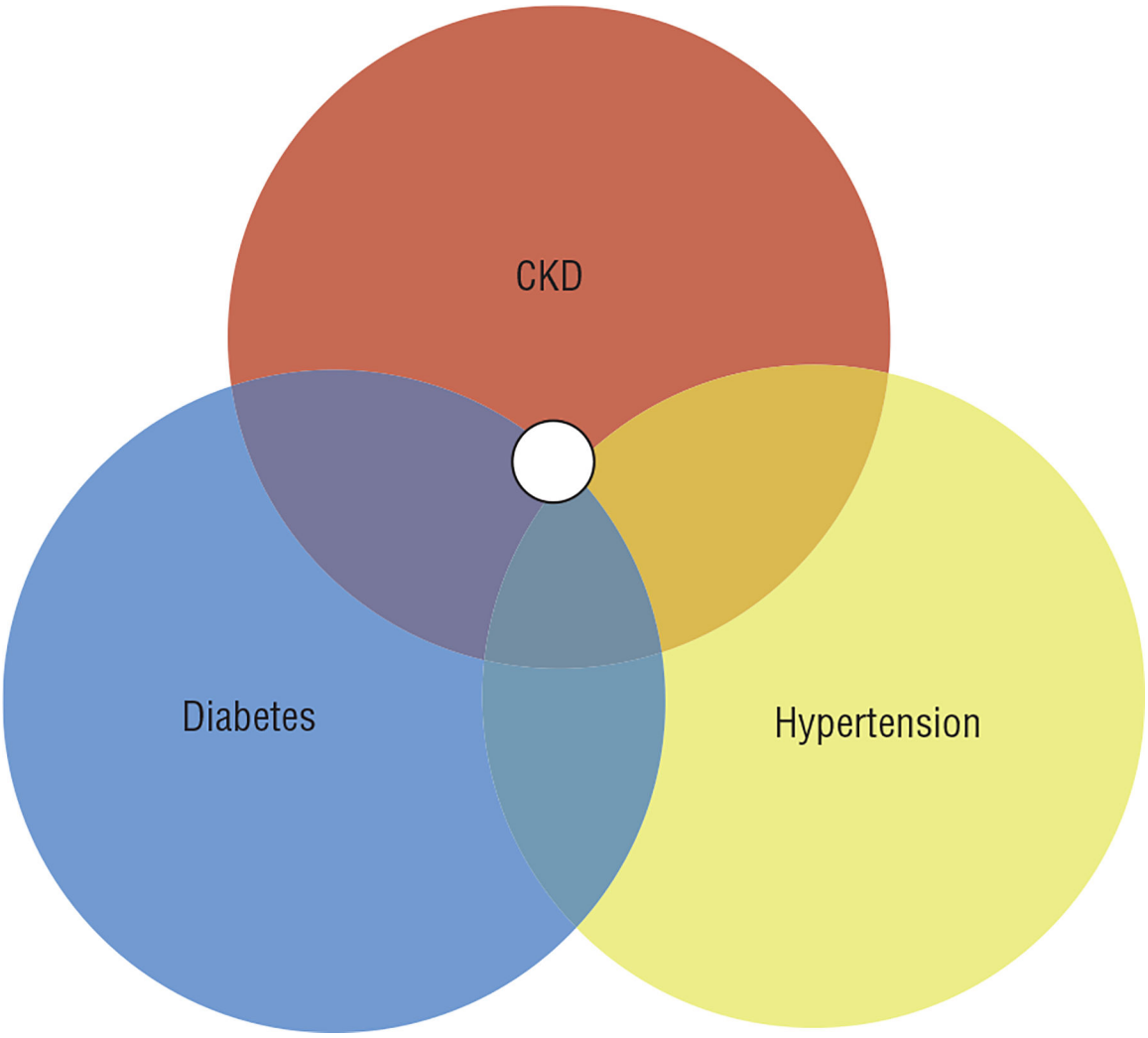

FIGURE 1.

Venn diagram demonstrating chronic kidney disease of nontraditional etiology (CKDnT) through the association of chronic kidney disease, diabetes, and hypertension

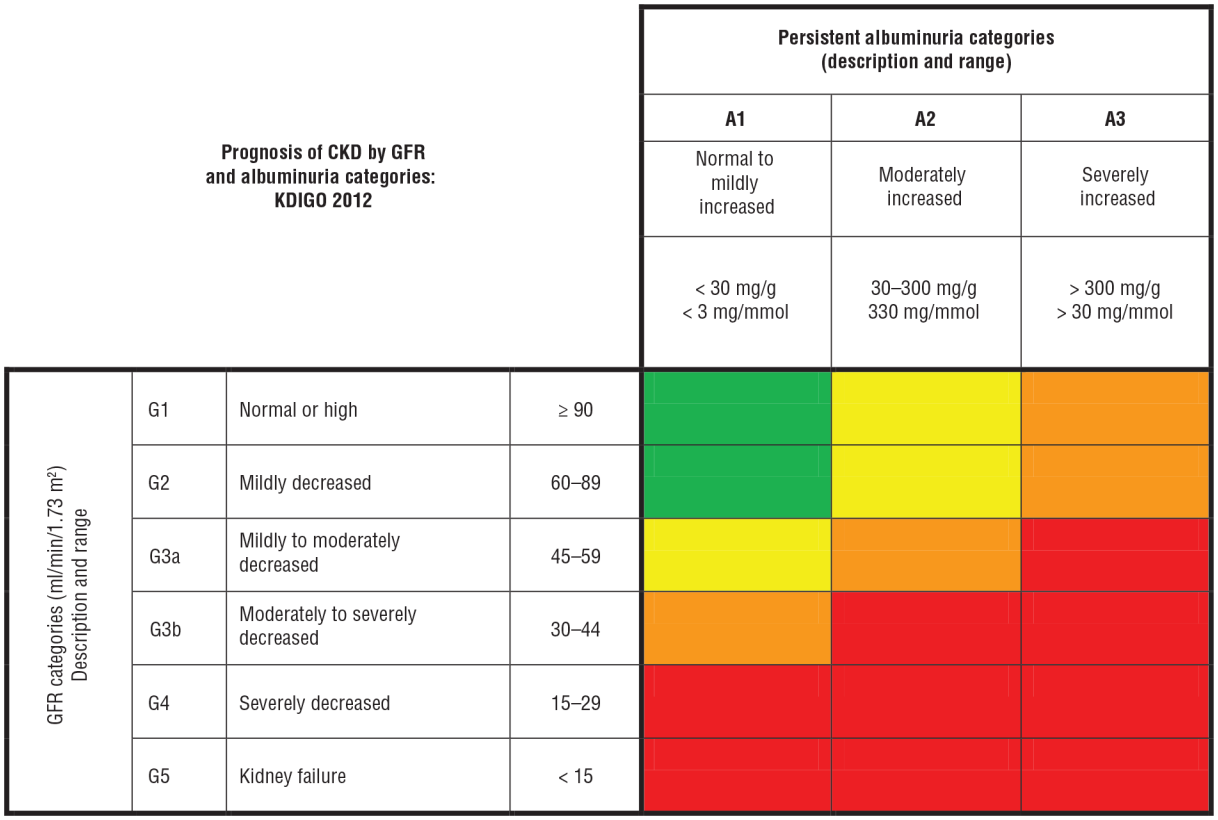

FIGURE 2. Kidney Disease: Improving Global Outcomes (KDIGO) stages of chronic kidney disease (CKD), with estimated glomerular filtration rate (GFR) and persistent albuminuria categories used to determine the risk level[a]

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

[a] Reprinted, with permission from Elsevier, from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.