



Confirmed clinical case of chronic kidney disease of nontraditional causes in agricultural communities in Central America: a case definition for surveillance

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ABSTRACT

Over the last 20 years, many reports have described an excess of cases of chronic kidney disease (CKD) in the Pacific coastal area of Central America, mainly affecting male farmworkers and signaling a serious public health problem. Most of these cases are not associated with traditional risk factors for CKD, such as aging, diabetes mellitus, and hypertension. This CKD of nontraditional causes (CKDnT) might be linked to environmental and/or occupational exposure or working conditions, limited access to health services, and poverty. In response to a resolution approved by the Directing Council of the Pan American Health Organization (PAHO) in 2013, PAHO, the U.S. Centers for Disease Control and Prevention, and the Latin American Society of Nephrology and Hypertension (SLANH) organized a consultation process in order to expand knowledge on the epidemic of CKDnT and to develop appropriate surveillance instruments. The Clinical Working Group from SLANH was put in charge of finding a consensus definition of a confirmed clinical case of CKDnT. The resulting definition establishes mandatory criteria and exclusion criteria necessary for classifying a case of CKDnT. The definition includes a combination of universally accepted definitions of CKD and the main clinical manifestations of CKDnT. Based on the best available evidence, the Clinical Working Group also formulated general recommendations about clinical management that apply to any patient with CKDnT. Adhering to the definition of a confirmed clinical case of CKDnT and implementing it appropriately is expected to be a powerful instrument for understanding the prevalence of the epidemic, evaluating the results of interventions, and promoting appropriate advocacy and planning efforts.

Key words

Renal insufficiency, chronic; agricultural workers' diseases; epidemiology; consensus development conference; Central America.

An epidemic of chronic kidney disease (CKD) is posing a serious public health problem for Central America (1). Over

the last two decades, Central America has reported as much as a 10-fold increase in the number of cases of people

suffering from CKD (2, 3). Among these cases, there have been reports of a type of CKD whose etiology is not related to the

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most frequent causes of CKD, such as diabetes mellitus and hypertension, and that constitutes what has been defined as “chronic kidney disease of nontraditional causes” (CKDnT) (1). In Central America, the age-standardized mortality rate attributable to CKD is higher than that observed in the rest of the Region of the Americas. Exhibiting an upward trend over time, the rate in some Central American countries has reached as high as 89.1 per 100 000 population (4-6).

Epidemiological context of kidney disease

CKD is a global public health problem. For example, data for the United States of America from the Third National Health and Nutrition Examination Survey show that approximately 13.1% of the adult population in the country present CKD (defined by a glomerular filtration rate of <60 ml/min/1.73 m² and/or an albumin-to-creatinine ratio of ≥30 mg/g) (7, 8).

At CKD stage 5D/5T [end-stage renal disease (ESRD)], renal replacement therapy (RRT) [dialysis (D) or kidney transplantation (T)] prolongs a patient's life. Between 2000 and 2010, the population on RRT increased steadily around the world. This growth was associated with an improvement in health coverage in developing countries, an increase in the life expectancy of individuals treated with dialysis or transplantation, and a rise in the frequency of traditional risk factors at the onset or progression of CKD: advanced age, diabetes, obesity, and hypertension (9).

According to the Latin American Registry of Dialysis and Transplantation, the prevalence of ESRD patients receiving RRT in Latin America has been steadily

growing over the last decade (10). However, RRT coverage of ESRD patients varies greatly between and within Latin American countries. In 2012, the overall RRT prevalence in 20 countries of Latin America was 661 per million population. The range was from 64 to 1 740 per million population, with the prevalence correlated positively with gross national income (11-13). As is true for other world regions, the increase in the prevalence of RRT in the Americas is largely, but not solely, related to improved access to therapy (9).

Chronic kidney disease in Central America

Epidemiology. In the specific case of Central America, very little information has been published about the frequency of CKD. Indeed, most of these countries have an incomplete national registry of dialysis or transplant, let alone of earlier stages of kidney disease (CKD stages 1 to 4). Data from the Latin American Registry of Dialysis and Transplantation showed that the prevalence of patients who were receiving RRT in 2012 in all the countries of Central America and the Spanish-speaking Caribbean (except Puerto Rico) was below the average for Latin America (13). However, the net burden of disease from CKD cannot be inferred solely on the basis of RRT prevalence data. That is because the prevalence of ESRD depends on the frequency of CKD itself and on access to health services, and survival depends on renal replacement therapy. Given this situation, along with limited data about the prevalence of CKD and ESRD or the known risk factors for CKD in the entire population, the net burden of

disease attributable to CKD is not well known in Central America.

Nevertheless, over the past 20 years there have been many published reports describing an excess of cases of CKD in the population of several countries in Central America—up to five times higher than the expected frequency for the age distribution (14-17). This increased frequency has been reported mainly in rural Pacific coast areas of the Central American countries of Costa Rica, El Salvador, Guatemala, and Nicaragua. The disease has primarily affected young men living in agricultural communities and working in the production of sugarcane, but also of bananas, cotton, and, to a lesser extent, subsistence crops such as corn, beans, and millet (16-18). In the affected areas, women have also had an increased prevalence of CKD, although to a much lesser extent. There is also some evidence that children from these areas may be at risk (16, 19). Studies have shown that CKDnT was probably present in the 1970s on the Pacific coast of Costa Rica, with a net increased prevalence of almost 10-fold in men and 4-fold in women by 2010 (2).

Risk factors. The increased frequency of CKD in some areas of Central America has reached epidemic proportions, but it does not seem to be associated with a rise in the frequency of traditional risk factors for kidney disease, such as diabetes, hypertension, or aging (14-19).

To date, no single etiological factor has been found responsible for the observed excess of CKD in this population. Many possible causes of CKDnT are cited in the scientific literature (Box 1). From a theoretical standpoint, based on evidence

BOX 1. Possible causes of chronic kidney disease of nontraditional causes, as cited in the scientific literature

1. Strenuous labor in extreme heat and humidity (heat stress), associated with dehydration, which could be conducive to repeated events of subclinical acute kidney damage; in addition, dehydration and exhausting work are associated with rhabdomyolysis (22, 28, 30, 34).
2. Renal toxicity linked to environmental and workplace contamination from agrochemicals (fertilizers, pesticides, and/or herbicides) (4, 15, 28, 29).
3. Heavy-metal contamination of food, the environment, and drinking water (31, 33, 37).
4. Food contamination by nephrotoxins (mycotoxins or some other toxins) (27).
5. Ingestion of potentially nephrotoxic drugs (herbal medicine, nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics) (16, 17, 25, 41).
6. Consumption of contaminated illegal alcohol (24).
7. Repeated infection by communicable tropical diseases (leptospirosis, malaria) (21, 33).
8. Chronic hyperuricemia and hypokalemia (23, 27).
9. Recurring urinary tract infections (16).

obtained from experimental and observational studies, it is hypothesized that the increased CKD frequency in some areas of Central America is associated with several risk factors, most likely acting in combination (20-34). These risk factors are suspected to be directly linked to environmental and occupational exposure, working conditions, limited access to health services, and poverty.

Factors such as social disadvantage, low birthweight, and poor access to health services may predispose to and intensify the impact of occupational and environmental factors (8, 32, 35). Identification of a rise in urinary excretion of biomarkers of kidney damage and a disproportionate increase in CKD frequency among adolescents suggests that the damage-causing mechanism could begin at a very early age in some patient groups (19). It is noteworthy that a similar clinical and epidemiological profile has been described in Egypt, India, and Tunisia, as well as extensively in the central-northern region of Sri Lanka (36, 37), which has climatic and sociodemographic characteristics similar to Central America.

It is unknown if the disease affects communities in other areas of Latin America. Some data from Brazil (22) and Mexico (38, 39) suggest that the epidemic of CKDnT may be occurring in those two countries as well.

Clinical picture. The most frequent clinical presentation is a slowly but steadily evolving deterioration in renal function. Occurring predominantly in male subjects, it begins in the second or third decade of life and involves minimal changes in urinalysis, normotensive or mildly hypertensive, an absence of peripheral edema, and no or low-grade proteinuria. Mild anemia, hypokalemia, and hyperuricemia are common. It constitutes a clinical-epidemiological entity that has been described elsewhere under various names, including Mesoamerican epidemic nephropathy, Central American nephropathy, and Salvadoran agricultural nephropathy (40, 41). Renal biopsy samples from patients with CKDnT have shown a pattern of predominant tubulointerstitial damage associated with glomerulosclerosis and, in some cases, signs of glomerular ischemia. This histopathological pattern could be the predominant finding of this entity (42, 43), which correlates well with the clinical findings.

Purpose of a definition of a confirmed clinical case of CKDnT

Most Central American countries lack reliable CKD registries or surveillance systems that are capable of detecting the disease's distribution patterns and morbidity and mortality trends. To characterize the clinical-epidemiological profile of the disease and identify risk factors at the population level, it is necessary to improve the epidemiological surveillance systems. In the specific case of CKDnT, a surveillance system that is community based and operated mainly by primary health care providers using a standard definition will be able to report cases of CKD that are detected at that level as suspected and probable cases of CKDnT, in defined population groups, in a given area and time (44). Subsequently, a probable case needs to be confirmed using established criteria (a "confirmed clinical case"). Health authorities can universally apply consensus criteria for the clinical confirmation of CKDnT cases in order to evaluate the frequency of the disease and its determinants, according to geographical area, age distribution, sociocultural factors, occupational and environmental factors, or other factors possibly associated with the disease.

METHODS

The Pan American Health Organization (PAHO), the U.S. Centers for Disease Control and Prevention (CDC), and the Latin American Society of Nephrology and Hypertension (SLANH) initiated a consultation process in October 2013, with the main objective of building knowledge on the CKDnT epidemic in Central America and of developing appropriate surveillance instruments. Those organizations took that action shortly after the PAHO Directing Council had approved PAHO Resolution CD52.R10, which dealt with chronic kidney disease in agricultural communities in Central America (45).

Pursuant to the provisions of the PAHO resolution, SLANH appointed a facilitator/coordinator for a working group charged with achieving a consensus definition for a confirmed clinical case of chronic kidney disease of nontraditional causes.

The coordinator called for the formation of a new Clinical Working Group, which was to be made up of a delegated

nephrologist designated from each national society of nephrology in Central America and in the Dominican Republic. Each of the selected persons had to have recognized clinical training, knowledge in the area of CKDnT, and public health training, as well as to have no direct or indirect conflicts of interest related to the study topic.

Once the Clinical Working Group delegates were appointed, they began remote consultations, following the Delphi method. The facilitator sent out a questionnaire to the experts, with instructions for them to gather their views about the epidemiology, clinical presentation, and diagnostic criteria for CKDnT, based on their personal opinions and experience or previous research. The delegates returned their answers to the facilitator, who then identified common and conflicting viewpoints.

The expert consultation was repeated for several more cycles. The facilitator controlled the interactions among the participants by processing the information and filtering out irrelevant content. A copy of the compiled documents was sent to each participant, who then had an opportunity to comment further. The process was stopped after the Clinical Working Group achieved a fundamental consensus.

A draft document was prepared that included the opinions of the experts and additional concepts that emerged from an expert narrative review that the facilitator did of most of the available literature about CKDnT published up to that point in indexed, peer-reviewed journals. The literature was identified through an extensive search in medical databases, including Scopus, PubMed, SciELO, and Google Scholar. Observational case series, epidemiological trials and reports, biopsy reports, opinions of experts, and editorials were included in the literature review.

Subsequently, an in-person workshop (mini-Delphi) was held to discuss and seek consensus on the draft document. The workshop was organized jointly by PAHO, CDC, SLANH, and the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA) and held in Guatemala City, Guatemala, on 16 and 17 December 2013. At that meeting, the discussion of the draft document continued from a strictly clinical and scientific standpoint. Suggestions were also made by members of

two other discussion groups that concurrently participated in the same workshop, to consider two related concerns: (1) the epidemiological definition of a suspected case of CKDnT and (2) reporting procedures and mortality coding. After an extended process of consultation with clinical experts, final editing of the consensus proposal was done with the participation of delegates from each organization. This process resulted in the final document forming the basis for the definition of a confirmed clinical case of CKDnT.

To establish the criteria for defining CKDnT, the most recent nephrology guidelines (8, 46, 47) were critically

analyzed by the Clinical Working Group, using the AGREE instrument (48). Relevant clinical manifestations of this entity were considered by the Clinical Working Group to establish the necessary "mandatory criteria" to define a case of CKD as CKDnT. The exclusion criteria were defined as the list of the most frequent causes of traditional CKD described in the medical literature.

RESULTS

For the primary purpose of having a definition of a clinical case of CKDnT for surveillance, every case of CKD will be classified as *confirmed* CKDnT if it meets

the *mandatory* criteria, in the absence of *exclusion* criteria (Box 2).

To complete the CKDnT epidemiological profile, in each case the following status should be recorded by the attending physician:

- 1) *Residing or having resided* for at least six months in an agricultural production area of Central America, establishing date and duration.
- 2) *Working or having worked* for at least six months in agricultural activities in Central America, establishing date and duration.

All cases of CKD that present one or more exclusion criteria are not classified

BOX 2. Mandatory criteria and exclusion criteria for classifying a patient as suffering from chronic kidney disease of nontraditional causes

1. **Mandatory criteria to classify a patient as having a confirmed clinical case of CKDnT:**
 - i. **Chronic kidney disease** (based on current consensus definition of CKD (3) and the clinical profile of CKDnT), defined and restricted to the following persistent alterations (for more than three months) with implications for health:
 - 1) Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² body surface area, preferably determined by the CKD-EPI formula, based on standardized serum creatinine, or in its absence, by the four-variable MDRD formula or the Cockcroft-Gault formula
and/or
 - 2) Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased eGFR:
 - A) non-nephrotic proteinuria (albuminuria >30 and <3 000 mg/24 hours, or albumin/creatinine ratio >30 and <3 000 mg/g)
and/or
 - B) urinary sediment abnormalities as markers of kidney damage (i.e., microscopic hematuria with abnormal erythrocytes morphology, or red blood cell casts, granular casts, or oval cells)
and/or
 - C) renal tubular disorders (i.e., renal tubular acidosis, nephrogenic diabetes insipidus, renal potassium wasting, other).
 - ii. **Age:** 2 to 59 years.
 - iii. **Ultrasonography of the urinary tract** demonstrating the presence of two morphologically symmetrical kidneys (eventually diminished in size), without urinary tract obstruction or renal polycystic disease.
 - iv. **Absence of any of the following exclusion criteria.**
2. **Exclusion criteria for classifying the CKD patient as having a confirmed clinical case of CKDnT:**
 - i. Clinical history of:
 - 1) **Diabetes mellitus** only if there is evidence of microangiopathy in other territories (diabetic retinopathy, diabetic neuropathy) or history (current or previous) of nephrotic proteinuria.
 - 2) **Hypertension:** JNC 7 stage 2 ($\geq 160/100$), or stage 1 hypertension with nonrenal target organ damage (cerebrovascular disease, ischemic heart disease, peripheral arteriopathy).
 - 3) **Urologic pathology** (i.e., verified nephrolithiasis, nonlithiasic obstructive nephropathy, surgical or traumatic reduction of renal mass, other).
 - 4) **Primary glomerulopathy** confirmed by renal biopsy or suspected due to presence of nephrotic-range proteinuria.
 - 5) **Hematologic disease** (i.e., multiple myeloma, systemic amyloidosis, lymphoma, leukemia, sickle cell anemia, other).
 - 6) **Genetic and/or hereditary renal disease** (i.e., Alport syndrome, polycystic renal disease, Fabry disease, familial glomerulopathy diagnosed by renal biopsy, other).
 - 7) **Autoimmune disease** (i.e., systemic lupus erythematosus, systemic or renal-limited vasculitis, rheumatoid arthritis, mixed connective tissue disease, Goodpasture syndrome, primary antiphospholipid syndrome, other).
 - 8) **Repeated exposure** to X-ray contrast media and/or administration of phospho-soda solutions, as preparation for colonoscopy.

In each case, record the following status:

 - 1) *Residing or having resided* for at least six months in an agricultural production area of Central America.
 - 2) *Working or having worked* for at least six months in agricultural activities in Central America.

in the group of CKDnT cases for epidemiological surveillance purposes.

It is not the purpose of these criteria to delve further into clinical diagnosis or exhaustive nosological research, which should be conducted by a specialist. Nevertheless, the Clinical Working Group made several recommendations:

- 1) Cases of CKDnT should be referred to the designated specialist, preferably a nephrologist, to complete the diagnosis (including kidney histopathology, if appropriate) and establish treatment guidelines.
- 2) It is suggested that CKD be classified by degree of decline in glomerular filtration rate and level of proteinuria or albuminuria (if present), according to the accepted international clinical practice guidelines (8).
- 3) It is recommended that clinical management and treatment of CKDnT cases be adapted to the best available evidence. Currently, the best strategy is to apply the recommendations in the SLANH CKD treatment guidelines for stages 1 to 5 and/or the KDIGO guidelines (8, 46).
- 4) Each case should be actively followed by a multidisciplinary team trained in the management of these patients, to evaluate the disease's progression and the benefit of therapeutic measures.
- 5) Surveillance of this entity should be encouraged in other countries in the Americas where it might be present.

DISCUSSION

Knowledge of the frequency of CKDnT and its geographical distribution, stage distribution, rate of progression, and associated risk factors is necessary for allocating resources, establishing public health policies at the community level, and developing kidney disease prevention programs.

In the absence of an etiological definition of CKDnT, operational criteria are needed to classify a CKD patient as a confirmed clinical case of CKDnT. These criteria should be easy to apply in large population groups and in conditions where health resources and access to the health care system are limited. These criteria should also be easily accepted by the community, ethically sound, and economically sustainable.

During the Clinical Working Group discussion process, several controversial

points arose. One was the name of the entity that is being defined. In the literature, various names are used that refer to the geographical area of the highest described frequency of CKDnT, affected occupations, or possible risks factors. At present, CKDnT nosology has not been well characterized, several population groups are involved, and the disease may not be confined to just Central America. Therefore, the Clinical Working Group decided to adopt, provisionally, the generic name of "chronic kidney disease of nontraditional causes" (CKDnT).

The second controversial point involved was establishing the mandatory criteria and exclusion criteria necessary for defining a case of CKD as CKDnT. The Clinical Working Group took into account universally agreed-upon definitions of CKD and significant clinical manifestations of this entity. Some cases of acute kidney injury (AKI) episodes may occur in the context of exposure to some of the risk factors associated with CKDnT, such as heat stress, dehydration, nonsteroidal anti-inflammatory drug consumption, acute toxicity, or urinary tract infection. The Clinical Working Group proposed following the KDIGO guidelines criteria of at least a three-month interval between two determinations of eGFR. The objective is to correctly classify a patient as a confirmed clinical case of CKDnT only if a reduction of kidney function persists over this time period. The three-month interval should not be required in the case of previous confirmed history of CKD and/or the presence of markers of chronicity (small or scarred kidneys demonstrated by image technology).

In addition, the list of exclusion criteria was defined as conditions that result in CKD as a consequence of the pathogenic process of the disease. These included the list of the most frequent causes of CKD associated with traditional risk factors or diseases that affect kidneys, as described in the medical literature. In the case of diabetes mellitus and hypertension, the definition includes evidence of target organ damage in addition to kidney involvement. Along the same lines, CKD prevalence increases with age over 60 years. This increased frequency is associated with the process of senescence and the associated increased frequency of traditional risk factors for CKD. This finding contrasts with the known epidemiology of CKDnT, which mostly affects younger people. Children less than 2 years old should be excluded, because the criterion

of eGFR <60 ml/min does not apply under this age, even adjusted for surface body area, and most CKD under this age is related to urinary tract malformation or developmental renal abnormalities.

In clinical practice, very often it is difficult to assign the main responsibility for kidney damage to a single risk factor or disease. Many times different factors, acting concurrently or sequentially, operate as the primary determinant, a progression factor, or a contributor to CKD. The current definition of CKDnT reserves the epidemiological classification to individuals effectively suffering from CKDnT as the primary disease, in an attempt to improve specificity. To establish whether CKDnT could contribute to the progression of CKD associated with other highly prevalent causes or vice versa is a subject of debate and study that is outside the scope of this definition for surveillance purposes. Building knowledge about the net contribution of CKDnT to the progression of other primary or secondary kidney diseases needs, first of all, proper characterization of CKDnT from an epidemiological and clinical point of view.

The third controversial point focused on the need to include urinary tract ultrasonography in the mandatory criteria (for diagnosis of a confirmed case of CKDnT). The Clinical Working Group established that, at present, urinary tract sonography is a simple, noninvasive diagnostic method that can be carried out with low-cost, portable equipment and can then be reported by technical personnel who have basic training in this area. At present, urinary tract sonography is considered integral to symptomatic assessment of the CKD patient. Urinary tract sonography is mandatory for ruling out causes of CKD that are associated with specific diseases (e.g., renal carcinoma, obstructive uropathy, or nephrolithiasis). The absence of diagnostic imaging could lead to misclassification of a patient as CKDnT (7, 8). Furthermore, the Clinical Working Group recommended that all patients should be referred, at least for first evaluation, to a designated specialist, preferably a nephrologist, or some other trained professional if a nephrologist is not available. A well-trained multidisciplinary team might not be present in many settings where CKDnT patients live. However, the evidence suggests that a multidisciplinary approach is critical to obtaining better clinical results, including a positive impact on disease progression, and even on disease regression (8). These recommendations apply to any patient with

CKD, and specifically to confirmed cases of CKDnT: To complete the study of the kidney disease, determine its stage, assess its rate of progression, and provide medical treatment based on the best available evidence. Finally, the Clinical Working Group specifically established the need for access to renal histopathology through renal needle biopsy, including optical microscopy and immunofluorescence, when deemed appropriate.

This clinical case definition of a confirmed case of CKDnT presents several strengths. First, it is based on universally accepted clinical and laboratory criteria for CKD. The definition includes, and is restricted to, particular aspects of the clinical presentation of CKDnT. Second, the definition should be easy to apply, especially in resource-constrained settings, thus avoiding the unneeded expenditure of limited health resources. Third, it will allow epidemiologists and clinicians to differentiate CKDnT from other causes of CKD, with an expected higher specificity. Finally, implementing the definition will allow public health decisionmakers to know the real impact and dimension of the CKDnT epidemic and to plan actions according to the distribution and causes of the disease (49, 50).

The main limitation of this case definition is the lack of an etiological knowledge of CKDnT. Despite this uncertainty, a case definition based on easily applied clinical criteria can become a useful tool for surveillance purposes and for expanding knowledge of CKDnT. The criteria established in the confirmed clinical case definition of CKDnT reflect the published evidence and clinical-epidemiological knowledge to date. However, as such, this case definition may be subject to change as the scientific knowledge of CKDnT develops. Finally, beyond the limitations and the provisional character of this definition, the most important concern is to have a definition that can be used as standard by all affected countries.

Conclusions

The consensus on the clinical definition of a confirmed case of chronic kidney disease of nontraditional causes is straightforward. The definition is primarily based on universally accepted clinical criteria, with the main purpose of the definition being to act as an instrument for health surveillance.

The Clinical Working Group members underscore the importance of

adhering to the definition of CKDnT and implementing it appropriately. Epidemiological surveillance grounded in consensus-based, universally accepted definitions of CKDnT will be a powerful instrument for learning about the pace of the epidemic in Central America and the results of interventions, as well as serve as an instrument for advocacy and planning. Finally, the Clinical Working Group also encourages epidemiological surveillance of CKDnT in other areas of the Americas where there might be cases.

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REFERENCES

- Pan American Health Organization. Chronic kidney disease in agricultural communities in Central America: concept paper. Washington, D.C.: PAHO; 2013. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=22051&Itemid=270&lang=en. Accessed 26 Sept 2016.
- Wesseling C, vanWendel de Joode B, Crowe J, Rittner R, Sanati NA, Hogstedt C, et al. Mesoamerican nephropathy: geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica. *Occup Environ Med*. 2015;72:714–21.
- Orantes CM, Herrera, Almaguer M. Epidemiology of chronic kidney disease in adults of Salvadoran agricultural communities. *MEDICC Rev*. 2014 Apr;16(2): 49–54.
- Ordunez P, Martinez R, Reveiz L, Chapman E, Saenz C, Soares da Silva A, et al. Chronic kidney disease epidemic in Central America: urgent public health action is needed amid causal uncertainty. *PLoS Negl Trop Dis*. 2014;8(8):e3019. doi:10.1371/journal.pntd.0003019.
- Pan American Health Organization. Chronic kidney diseases (N18) & Renal failure (N17-N19) mortality, countries of the Americas. Age-standardized mortality rate per 100,000 population. Available from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=9402/. Accessed 17 July 2016.
- Ordunez P, Saenz C, Martinez R, Chapman E, Reveiz L, Becerra F. The epidemic of chronic kidney disease in Central America. *Lancet Glob Health*. 2014. doi: [http://dx.doi.org/10.1016/S2214-109X\(14\)70217-](http://dx.doi.org/10.1016/S2214-109X(14)70217-). Accessed 12 August 2016.
- Coresh J, Selvin E, Stevens A. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007 Nov. 7;298(17): 2038–47.
- KDIGO. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements* (2013) 3, Issue 1. Available from: http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Accessed 18 July 2016.
- Robinson BM, Akizawa T, Jager KJ, Kerr PG, Saran R, Pisoni RL. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and hemodialysis practices. *Lancet*. 2016;388:294–306.
- Gonzalez-Bedat M, Rosa-Diez G, Pecoits-Filho R, Ferreiro A, García-García G, Cusumano A, et al. Burden of disease: prevalence and incidence of ESRD in Latin America. *Clin Nephrol*. 2015;83(7 Suppl 1):S3–S6.
- Cusumano A, García García G, Gonzalez Bedat C. The Latin American Dialysis and Transplant Registry: report 2006. *Ethn Dis*. 2009;19(1 Suppl 1):S1–3.
- Rosa-Diez G, Gonzalez-Bedat M, Pecoits-Filho R, Marinovich S, Fernandez S, Lugon J, et al. Renal replacement therapy in Latin American end-stage renal disease. *Clin Kidney J*. 2014;0:1–6. doi: 10.1093/ckj/sfu039.
- Rosa-Diez G, Gonzalez-Bedat M, Ferreiro A, García-García G, Fernandez-Cean J, Douthat W. Burden of end-stage renal disease (ESRD) in Latin America. *Clinical Nephrology*. 2016 Aug 10;85(1):S1–5.
- Ramirez-Rubio O, Mc Clean M D, Amador JJ, Brooks DR. An epidemic of chronic kidney disease in Central America: an overview. *J Epidemiol Community Health*. 2013 Jan; 67:1–3.
- García Trabanino R, Aguilar R, Silva CR, Mercado MO, Merino RL. End-stage renal disease among 30 patients in a referral hospital in El Salvador. *Rev Panam Salud Publica* 2002;12(3):202–6.
- Torres C, Aragon A, González M, Lopez I, Jakobsson K, Elinder C, et al. Decreased

- kidney function of unknown causes in Nicaragua: a community-based survey. *Am J Kidney Dis.* 2010;55(3):485–96.
17. Peraza S, Wesseling C, Aragon A, Leiva R, García-Trabanino R, Torres C, et al. Decreased kidney function among agricultural workers in El Salvador. *Am J Kidney Dis.* 2012;59(4):531–40.
 18. Laux TS, Bert PJ, Barreto Ruiz GM, González M, Unruh M, Aragon A, et al. Nicaragua revisited: evidence of lower prevalence of chronic kidney disease in a high-altitude, coffee-growing village. *J Nephrol.* 2012;25(4):533–40.
 19. Ramirez-Rubio O, Amador JJ, Kaufman JS, Weiner DE, Parikh CR, Khan U, et al. Urine biomarkers of kidney injury among adolescents in Nicaragua, a region affected by an epidemic of chronic kidney disease of unknown aetiology. *Nephrol Dial Transplant.* 2016;31:424–32.
 20. O'Donnell JK, Tobey M, Weiner DE, Stevens LA, Johnson L, Stringham P, et al. Prevalence of and risk factors for chronic kidney disease in rural Nicaragua. *Nephrol Dial Transplant.* 2011;26(9):2798–805.
 21. Orantes CM, Herrera R, Almaguer M, Brizuela EG, Hernández CE, Bayarre H, et al. Chronic kidney disease and associated risk factors in the Bajo Lempa region of El Salvador: Nefrolempa study, 2009. *MEDICC Rev.* 2011;13(4):14–22.
 22. Santos UP, Zanetta DM, Terra-Filho M, Burdmann EA. Burnt sugarcane harvesting is associated with acute renal dysfunction. *Kidney Int.* 2015;87:792–9.
 23. Roncal Jimenez CA, Ishimoto T, Lanaspá MA, Rivard CJ, Nakagawa T, Ejaz AA, et al. Fructokinase activity mediates dehydration-induced renal injury. *Kidney Int.* 2014 Aug;86(2):294–302.
 24. Sanoff SL, Callejas L, Alonso CD, Hu Y, Colindres RE, Chin H, et al. Positive association of renal insufficiency with agriculture employment and unregulated alcohol consumption in Nicaragua. *Ren Fail.* 2010;32(7):766–77.
 25. Ramirez-Rubio O, Brooks DR, Amador JJ, Kaufman JS, Weiner DE, Scammell MK. Chronic kidney disease in Nicaragua: a qualitative analysis of semi-structured interviews with physicians and pharmacists. *BMC Public Health.* 2013;13:350. Available from: <http://www.biomedcentral.com/1471-2458/13/350/>. Accessed 18 July 2016.
 26. Cerdas M. Chronic kidney disease in Costa Rica. *Kidney Int Suppl* 2005;97: S31–S33.
 27. Weiner DE, McClean MD, Kaufman JS, Brooks DR. The Central American epidemic of CKD. *Clin J Am Soc Nephrol.* 2013;8(3):504–11.
 28. Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for a Mesoamerican nephropathy. *Am J Kidney Dis.* 2014 Mar; 63(3):506–20.
 29. Azaroff LS. Biomarkers of exposure to organophosphorous insecticides among farmers' families in rural El Salvador: factors associated with exposure. *Environ Res.* 1999 Feb 28;80(2):138–47.
 30. Delgado Cortez O. Heat stress assessment among workers in a Nicaraguan sugarcane farm. *Glob Health Action.* 2009. doi: 10.3402/gha.v2i0.2069.
 31. Mc Clean M, Amador JJ, Laws R, Kaufman J, Weiner D, Sánchez JM, et al. Biological sampling report: investigating biomarkers of kidney injury and chronic kidney disease among workers in Western Nicaragua. Boston: Boston University School of Public Health; 2012. Available from: http://www.cao-ombudsman.org/documents/Biological_Sampling_Report_April_2012.pdf/. Accessed 18 July 2016.
 32. Kjellstrom T, Crowe J. Climate change, workplace heat exposure, and occupational health and productivity in Central America. *Int J Occup Environ Health.* 2011 Jul-Sep;17(3):270–81.
 33. Soderland P, Lovekar S, Weiner D, Brooks DR, Kaufman J. Chronic kidney disease associated with environmental toxins and exposures. *Adv Chronic Kidney Dis.* 2010 May 31;17(3):254–64.
 34. Glaser J, Lemery J, Rajagopalan B, Diaz HF, García-Trabanino R, Tadini G, et al. Climate change and the emergent epidemic of CKD from heat stress in rural communities: the case for heat stress nephropathy. *Clin J Am Soc Nephrol.* 2016 May. Published Ahead of print. doi: 10.2215/CJN.13841215.
 35. Garcia-Garcia G, Jha V. CKD in disadvantaged populations. *Clin Kidney J.* 2015;8:3–6.
 36. Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. *Nat Rev Nephrol.* 2013;9, 278–90.
 37. Jayasumana M, Paranagama P, Amarasinghe MD, Wijewardane KM, Dahanayake KS, Fonseka SI, et al. Possible link of chronic arsenic toxicity with chronic kidney disease of unknown etiology in Sri Lanka. *J Nat Sci Res.* 2013;3(1).
 38. Mendoza-González MF, Montes-Villaseñor E, Muñoz-Flores P, Salado-Pérez MR, Espejo-Guevara DM, Tapia-Jaime G. Prevalencia de enfermedad renal crónica en una población de alto riesgo. Tierra Blanca, Veracruz, México. 2012. Available from: <http://www.convencionalud2012.sld.cu/index.php/convencionalud/2012/paper/view/1759/816>. Accessed 26 Sept 2016.
 39. Consultores Ambientales Asociados SC. Insuficiencia renal crónica en Tierra Blanca Veracruz, 1998–2003. Available at: <http://www.greenpeace.org/mexico/Global/mexico/Docs/2013/resumen%20ejecut%20Tierra%20Blanca%202007.pdf>. Accessed 18 July 2016.
 40. Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D, eds. Mesoamerican nephropathy: report from the First International Research Workshop on MeN. Heredia, Costa Rica: SALTRA/IRET-ONE; 2013. Available from: <http://www.saltra.una.ac.cr/images/SALTRA/Documentacion/SerieSaludTrabajo/seriesaludytrabajo10.pdf>. Accessed 23 January 2015.
 41. Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH. Resolving the enigma of the Mesoamerican nephropathy: a research workshop summary. *Am J Kidney Dis.* 2014 Mar;63(3):396–404. doi: 10.1053/j.ajkd.2013.08.014. Epub 2013 Oct 17.
 42. Wijkström J, Leiva R, Elinder CG, Leiva S, Trujillo Z, Trujillo L, Söderberg M, et al. Clinical and pathological characterization of Mesoamerican nephropathy: a new kidney disease in Central America. *Am J Kidney Dis.* 2013 Nov;62(5):908–18.
 43. López-Marín L, Chávez Y, García X A, Flores WM, García, YM, Herrera R, et al. Histopathology of chronic kidney disease of unknown etiology in Salvadoran agricultural communities. *MEDICC Rev.* 2014 April;16(2): 49–54.
 44. Lozier M, Turcios-Ruiz R, Noonan G, Orduñez P. Chronic kidney disease of non-traditional etiology in Central America: a provisional epidemiologic case definition for surveillance purposes and epidemiologic studies. *Rev Panam Salud Publica.* 40(5):294–300.
 45. Pan American Health Organization. Resolution CD52.R10. Chronic kidney disease in agricultural communities in Central America. Washington, D.C.: PAHO; 2013. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=23347&Itemid=270&lang=en. Accessed 25 Sept 2016.
 46. Obrador-Vera GT, Correa-Rotter R, Aguilar MA, Bellorin-Font E, Burgos Calderón R, Carlini R, et al. Guías latinoamericanas de práctica clínica sobre la prevención, diagnóstico y tratamiento de los estadios 1-5 de la enfermedad renal crónica. Available from: <http://www.fundrenal.org.mx/guia>. Accessed 19 October 2014.
 47. Canzani O, De Souza N, Gadola L, Lamadrid V, Rios P, Schwedt E, et al. Guías de práctica clínica en el diagnóstico y tratamiento de la enfermedad renal crónica. Available from: [http://www.fnr.gub.uy/sites/default/files/publicaciones/FNR_guias_practica_clinica_ERC_2013_tapa.pdf/](http://www.fnr.gub.uy/sites/default/files/publicaciones/FNR_guias_practica_clinica_ERC_2013_tapa.pdf). Accessed 18 July 2016.
 48. Consorcio AGREE. Instrumento AGREE II. Instrumento para la evaluación de guías de práctica clínica. Available from: http://www.guiasalud.es/contenidos/documentos/Guías_Practica_Clinica/Spanish-AGREE-II.pdf/. Accessed 18 July 2016.
 49. Kjellstrom T. Climate change, direct heat exposure, health and well-being in low and middle-income countries. *Glob Health Action* 2009. doi: 10.3402/gha.v2i0.1958.
 50. Silva LC, Ordúñez P. Chronic kidney disease in Central American agricultural communities: challenges for epidemiology and public health. *MEDICC Rev.* 2014 April;16(2):66–71.

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RESUMEN**Caso clínico confirmado de enfermedad renal crónica de causas no tradicionales en comunidades agrícolas de Centroamérica: una definición de caso para la vigilancia**

En los 20 últimos años, en muchos informes se ha descrito un número inusual de casos de enfermedad renal crónica (ERC) en la costa del Pacífico de Centroamérica, que afecta principalmente a trabajadores agrícolas varones y señala un grave problema de salud pública. La mayoría de estos casos no se asocia con los factores de riesgo tradicionales de ERC, como envejecimiento, diabetes mellitus e hipertensión. Esta ERC de causas no tradicionales (ERCnT) podría estar vinculada con la exposición laboral o ambiental o las condiciones de trabajo, el escaso acceso a los servicios de salud y la pobreza. En respuesta a una resolución aprobada por el Consejo Directivo de la Organización Panamericana de la Salud (OPS) en el 2013, la OPS, los Centros para el Control y la Prevención de Enfermedades de los Estados Unidos y la Sociedad Latinoamericana de Nefrología e Hipertensión (SLANH) organizaron un proceso de consulta para ampliar los conocimientos sobre la epidemia de ERCnT y elaborar instrumentos apropiados para la vigilancia. El Grupo Clínico de Trabajo de la SLANH tuvo la responsabilidad de consensuar una definición de caso clínico confirmado de ERCnT. En la definición resultante se establecen criterios obligatorios y criterios de exclusión necesarios para clasificar un caso como de ERCnT. La definición incluye una combinación de definiciones de ERC universalmente aceptadas y las principales manifestaciones clínicas de ERCnT. Sobre la base de los mejores datos científicos disponibles, el Grupo Clínico de Trabajo también formuló recomendaciones generales acerca del manejo clínico, que se aplican a cualquier paciente con ERCnT. Se espera que la adopción de la definición de caso confirmado de ERCnT y su aplicación adecuada sean una herramienta poderosa para conocer la prevalencia de la epidemia, evaluar los resultados de las intervenciones y promover acciones apropiadas de sensibilización y planificación.

Palabras clave

Insuficiencia renal crónica; enfermedades de los trabajadores agrícolas; epidemiología; conferencia de consenso; América Central.