REPORT FROM THE
FOURTH INTERNATIONAL WORKSHOP ON CHRONIC KIDNEY DISEASE OF UNKNOWN ETIOLOGY (CKDu)

Executive Summary

February 14-16, 2024
Antigua Guatemala

Nathan Raines, Marvin González-Quiroz, Jennifer Crowe, Dan Brooks,
Vicente Sánchez-Polo, Vidhya Venugopal, Carl-Gustaf Elinder, Gerardo Arroyo,
Karen Courville, Anna Strasma, Ben Caplin (editors)

INTRODUCTION

Chronic Kidney Disease of Unknown Cause (CKDu) is a novel form of CKD, primarily affecting young individuals engaged in strenuous labor in hot climates and low socioeconomic settings. CKDu is not associated with common antecedent conditions such as hypertension, diabetes, or systemic autoimmunity. Patients often present without hematuria or proteinuria, and limited kidney biopsies usually reveal chronic tubulointerstitial nephritis. The etiology of CKDu remains incompletely understood. While heat stress is a well-supported risk factor in certain populations, there may be alternative or interacting contributors to disease such as environmental exposures, nephrotoxic medications, infections, and genetic predisposition. CKDu prevalence is notably high in Central America and Mexico, particularly in agricultural regions. A similar pattern of CKDu exists in South Asia.

The Fourth International Workshop on Chronic Kidney Disease of Unknown Cause (CKDu), held from February 14 to 16, 2024, in Antigua Guatemala, Guatemala, marked a significant collaborative effort among leading health organizations and researchers from 16 countries. The Consortium for the Epidemic of Nephropathy in Central America and Mexico (CENCAM) organized the workshop in partnership with the Executive Secretariat of the Council of Ministers of Health of Central America and the Dominican Republic (SE-COMISCA), the Latin American Society of Nephrology and Hypertension (SLANH), The Central American Program for Health, Work and Environment (SALTRA), and the Spanish Agency for International Development Cooperation (AECID).

The organizing committee aimed to engage diverse perspectives in a friendly and inclusive discussion between researchers in CKDu hotspot regions as well as international experts. By fostering an atmosphere that welcomed a variety of skills, interests, disciplines, countries, and viewpoints, the workshop facilitated comprehensive and collaborative dialogue on CKDu. During the workshop, participants were divided into working groups to address key questions surrounding CKDu, focusing on causality, research methods, population identification, stakeholder collaborations, clinical insights, patient voices, and basic sciences.

These discussions were essential for advancing our understanding of CKDu and informing the project "Apoyo a la Implementación de la Estrategia para la Prevención, Mitigación y Control de la Enfermedad Renal Crónica de Origen no Tradicional (ERCnt) en Centroamérica y República Dominicana". (Support for the Implementation of the "Strategy for the Prevention, Mitigacion and Control of Chronic Kidney Disease of non-traditional Origin (CKDnt)" In accordance with the missions of CENCAM, SLANH, and SALTRA, we aim to enhance the prevention, mitigation, and control of CKDu across affected regions, fostering a collaborative approach to tackling this enigmatic disease. The workshop's

recommendations aim to inform policy makers, researchers, healthcare providers and community members with a particular emphasis on enhancing educational programs in CKDu-affected regions.

This document includes:

1. This executive summary provides an overview of themes, areas of scientific consensus, and places where uncertainty remains. Individual topic-based working group summaries provide further detail about recommendations from the each working group, and are available in the document "Fourth International Workshop on CKDu: Topic-Based Working Groups

2. ALTERNATIVELY, you could combine this document and the topic-based working groups document into one document, with the topic-based working groups falling after the executive summary. This might parallel the country-based working group document structure, which has an executive summary followed by the individual working group documents.

WORKING GROUPS AND PARTICIPANTS:

OVERALL CAUSALITY

Marvin González Quiroz, Nathan Raines, Daylin Anchía, Ali Al-Rashed, Daniel Brooks, David Friedman, David Flood, Danny Gómez, Peter Rohloff, Hair Romero

HEAT EXPOSURE AND INTERVENTIONS

Erik Hansson, Alex Alberto Cruz Aguilar, Daniel Olson, Emmanuel Jarquín, Grant Tore, Lyndsay Krisher, Miriam Eugenia Brenes Cerdas, Madeleine Scammell, Rebekah Lucas, Zachary Schlader, Jocelyn Fimbres, Miranda Dally, Kathy James, Sandra Peraza

ENVIRONMENTAL EXPOSURES

Carl Gustaf Elinder, Lesliam Quirós-Alcalá, Jose Manuel Arreola Guerra, Ana Evelia Rodas Aguilar, Channa Jayasumana, Jessica Leibler, Mariela Betzabé Guerra García, Melissa DeSantiago, Nicole Villegas González, Sandra Cortés, Selene Vences, Federico Moncada Chevez¸ Magda Hernandez, Shuchi Anand

ANALYTICAL EPIDEMIOLOGY

David H. Wegman, Magdalena Madero, Ben Caplin, Sophie Claudel, Rebecca Fischer, Rolando Herrero-Acosta, Christer Hogstedt, Indiana López-Bonilla, Viviana Loria-Carvajal, Dinesh Neupane, Maria Isabel Pedroza-Estrada, Ana Leonor Rivera-Chavarría, Dilcia Esperanza Sauceda- Acosta, Ajay Singh, Anna Strasma

MÉTODOS CUALITATIVOS: VOCES DE LOS PACIENTES Y COMUNIDADES

Oriana Ramirez Rubio, Randall Lou Meda, Carolina Guzmán Quilo, Angie Aguilar-González, Jessica Saína Díaz Matute, Karely Villarreal Hernandez, Mirna Margarita Ramirez Rivera, Damaris Lopez Pilarte, Iris Delgado

BASIC SCIENCE/OMICS

Amin Oomatia, Jared Brown, Werner González, Diane Santos, Iván Landires, Sushrut Waikar, Eugenio Vilanova Gisbert, Samira Salihovic, Samantha Hall, Yeimy Herrera

HISTOPATHOLOGY

Carmen Ávila-Casado, Julia Wijkström, Manuel Cerdas, Zulma Cruz, Werner de León , Annika Östman Wernerson, Carmen Cajina-Aguirre

SURVEILLANCE AND SCREENING

Aurora Aragón, Gerardo Arroyo, Neil Pearce, Berta Sam Colop, Charlotte Rutter, Kristina Jacobson, Thais Mayorga Acosta, Joaquín Barnoya, Andrea Corrales, Pedro Dávila, Adriana Torres Moreno

CLINICAL DIAGNOSIS AND MANAGEMENT

Karen Courville, Vicente Sánchez Polo, Marta Avellán, Ramón García, Ricardo Leiva, Luis Ramírez

WORK THAT INVOLVES BOTH GOVERNMENT/PUBLIC HEALTH SYSTEMS AND RESEARCHERS

Jennifer Crowe, Ricardo Correa-Rotter, María de los Ángeles Campos, María Inés Esquivel, Nelson García Salazar, Hildaura Acosta, Jesica Candanedo P, Mónica Espinoza, René Santos, María Isabel Pedrosa, Guillermo Álvarez Álvarez, Claudio Monge

WORK INVOLVING INDUSTRY AND RESEARCHERS

Jason Glaser,Vidhya Venugopal, Juan Carlos Fernandez Quezada, Lourdes Doniz Lima, Julieta Granados Ramírez, Denis Chavarría, Thomas Boswell, John Adgate, Lee Newman, Ines Amenabar, Heath Prince

EXECUTIVE SUMMARY OF WORKING GROUP DISCUSSIONS FROM THE FOURTH INTERNATIONAL WORKSHOP ON CKDU

1. WHAT CAUSES CKDU?

1.1. There is no simple answer to what "causes" CKDu. Important risk factors for kidney decline in populations at risk of CKDu have been identified, however the etiology of disease remains inadequately understood.

1.2. Multiple factors are likely to contribute to CKDu, either independently, at different timepoints in the course of disease, perhaps together and/or in combination. Identified risk factors, for at least some affected populations include:

1.2.1. Social determinants of health. In particular, factors linked to poverty and low educational level are likely an important root cause of disease.

1.2.2. Occupational heat stress. Heat stress has been shown to worsen kidney function in the population at risk of CKDu. Furthermore, evidence suggests simple interventions such as rest-shade-hydration can reduce the impact of work-related heat exposure on kidney function decline.

1.3. CKDu, as it is currently defined, may be caused by different disease mechanisms in different individuals and/or populations. Not all factors may be needed in all individuals and the importance of different factors may vary by region.

1.4. There remains a range of opinions amongst experts as to the relative importance of different causal factors and the potential for additional factors to be identified that contribute substantially to disease. Rigorous and generalizable research studies aimed at exploring potential causal factors continue to be important, ideally with methodologies that allow for comparisons across CKDu-affected regions.

1.5. Despite the incomplete understanding of CKDu causality, implementing interventions aimed at protecting individuals against disease, by reducing exposure to known or suspected risk factors, is possible and should be prioritized (see Section 2.5).

2. HOW DO WE LEARN MORE ABOUT CKDU AND ITS CAUSES, PREVENTION AND TREATMENT?

2.1. Individuals and organizations from the public health, government, industry and academia interested in addressing or understanding CKDu should engage with multidisciplinary research teams, using existing networks like CENCAM and SALTRA, to ensure a scientifically sound research strategy that builds on existing knowledge about the disease.

2.2. We recommend the use of community participatory research and qualitative methods alongside quantitative studies. These methods can be a pathway to improving access to, and quality of, healthcare, promote occupational health and reduce work-related risks.

2.3. We need to better understand the burden of CKDu. While CKDu represents a significant public health challenge within chronic non-communicable diseases, many countries lack dedicated surveillance programs for CKDu.

2.3.1. Useful estimates of disease burden can be obtained from one or more of: existing health surveillance systems, disaggregation of national mortality statistics, focused monitoring systems and periodic population surveys using standardized protocols.

2.3.2. Early detection through routine screening for CKDu, particularly in high-risk populations or in areas acknowledged to be hotspots is of particular importance both to understand the burden of disease and allow for early intervention.

2.3.3. Efforts to standardize reporting practices, establish a uniform registry system, and inclusion of CKDu cases in compulsory disease notification systems should be supported.

2.4. We recommend reexamination of the current definitions of CKDu proposed by PAHO. For example, CKDu can also affect non-agricultural workers, and these individuals are excluded from the current definition.

2.5. Evaluation of interventions to reduce disease burden is critical to widespread implementation of measures that reduce the impact of CKDu.

2.5.1. Detection of early disease is critical to understand interventions that limit CKDu development or progression. Measures based on serum creatinine (used to estimate glomerular filtration rate) are currently the most useful and practical.

2.5.2. A definition based on modified Kidney Disease Improving Global Outcomes criteria, i.e., an increase in serum creatinine by 0.3 mg/dl or 1.5x baseline over the study period (which investigators have termed 'incident kidney injury') is appropriate for such evaluations.

2.5.3. Better early clinical markers of disease are needed. Ideal markers would be cheap, easy to measure, non-invasive, have low-technical needs, and be broadly accepted and widely implementable.

2.5.4. Implementation research to study the effectiveness of interventions aimed at mitigating heat stress should be prioritized to understand why evidence-based interventions can produce varied results when applied in real-world scenarios.

2.5.5. Interventions aimed at reducing the use of medications known to have nephrotoxic effects are needed to identify whether this represents an additional opportunity to reduce burden of disease.

2.6. Studies of the etiology of CKDu are extremely challenging due to problems observing surrogates of early disease and robustly measuring exposure. A broad variety of research methodologies may be appropriate, and we encourage countries to continue to engage with ongoing research on CKDu causality through international, interdisciplinary research. CENCAM, SALTRA and SLANH can provide support to governmental agencies and researchers interested in linking research results to policy.

2.7. Histopathology investigation remains a key component of advancing our understanding of CKDu.

2.7.1. The ultimate goal should be to establish specialized centers for performing kidney biopsies in each country affected by CKDu; however, support is required for the development of the infrastructure, with equipment for pathology laboratories and renal pathologist training.

2.7.2. Collaboration with existing international nephrology societies and development of new partnerships and programs is essential.

2.7.3. A standardized renal biopsy template, an educational atlas of CKDu histopathology, and research biobanks to sit alongside a disease registry may also allow us to improve our understanding of disease.

2.8. Application of newer scientific techniques in CKDu research, including study of DNA and RNA, metabolites and proteins, may contribute to improved understanding of environmental exposures, susceptibility, causation, diagnosis, prognosis, and treatment.

3. HOW CAN DIFFERENT STAKEHOLDERS WORK TOGETHER EFFECTIVELY TO ADDRESS CKDU?

3.1. The proactive involvement of patients and affected communities is essential, including community councils and leaders (including indigenous governance structures where relevant), patient associations, unions and worker associations, community health agents/workers, health councils, education professionals and family associations.

3.2. We advocate improving communication between researchers, patients and community members, medical and public health professionals, industry, and government agencies to support evidence-based decision-making and the implementation of actions aimed at reducing the burden of CKDu.

3.3. Overall, provision of basic public health needs (including access to safe drinking water and healthcare, worker health and safety, interventions to enhance maternal wellbeing, and healthy diet) will likely reduce population-level susceptibility to CKDu.

3.4. The interdisciplinary and multiprofessional training of primary care and community health professionals in the area of CKDu should be prioritized. They should be integrated into existing training programs that are broadly applicable across multiple CKDu-endemic regions. Specific considerations for individual areas can be included as addenda to the overall training program.

3.5. Community education programs to promote prevention and management of CKDu should be established or expanded with active involvement from both education professionals and affected communities. These programs should draw from existing resources where possible, and aim to be broadly applicable across the region, and individualized to specific areas when necessary.

3.6. Alongside the ethical responsibility to improve occupational health systems for workers, collaboration between industry, workers, clinicians and researchers can yield substantial benefits for all stakeholders across multiple domains (e.g., health, productivity, research).

3.6.1. Employers of workers exposed to heat stress need to be informed about links between heat stress and CKDu, occupational heat stress prevention, and be able to recognize signs and symptoms of heat stress.

3.6.2. Consideration must be given to informal and migrant laborers who can be susceptible to exploitation.

4. WHAT DO CLINICIANS WHO TAKE CARE OF CKDU PATIENTS SAY ABOUT THE DISEASE?

4.1. Diagnosis of CKDu is challenging and relies on a high-level of clinical suspicion as the cause remains unknown and there are no specific tests for this disease.

4.1.1. Be aware that the disease is often asymptomatic.

4.1.2. Early detection and diagnosis allow for effective management, including ongoing monitoring and interventions to prevent progression.

4.1.3. It is important to have a high level of suspicion if the patient lives or with works in an endemic area, regardless of whether he or she does not practice agriculture, since it is a disease that is not exclusive to this occupation.

4.2. Promoting healthy behaviors such as maintaining optimal weight, avoiding heat exposure, staying hydrated, and refraining from cigarette smoking are likely to be beneficial.

4.3. Other health conditions associated with kidney disease will often co-exist in populations with CKDu. Management of conditions such as hypertension and diabetes must also be a priority.

4.4. Adequate supportive care to manage the advanced stages of disease including symptoms of fatigue and anemia as well as potentially offering dialysis or kidney transplant options should be prioritized in CKDu endemic regions.


CENCAM

SLANH

SALTRA

MINISTERIO
DE ASUNTOS EXTERIORES, UNIÓN EUROPEA
Y COOPERACIÓN

Cooperación
Española

SECRETARÍA EJECUTIVA
COMISCA

SICA
Sistema de la Integración
Centroamericana