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MESOAMERICAN NEPHROPATHY

Report from the *Second* International Research Workshop on MeN

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MESOAMERICAN NEPHROPATHY

Report from the ***Second*** International Research Workshop on MeN

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MESOAMERICAN NEPHROPATHY

Report from the ***Second*** International Research Workshop on MeN

Bringing together knowledge, research questions, and initiatives related to Chronic Kidney Disease of unknown origin in Mesoamerica

NOVEMBER 18-20, 2015 HOTEL AUROLA HOLIDAY INN, SAN JOSÉ, COSTA RICA

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MAIN MESSAGE

There is general scientific consensus based on multiple studies by different research groups in several countries that Mesoamerican Nephropathy has a predominantly occupational component. There is growing evidence for a causal role of strenuous work, heat and insufficient rehydration as risk factors in MeN, and progress has been made towards clarifying pathophysiological pathways for heat stress leading to chronic kidney disease. Intervention studies are warranted to reduce heat stress and dehydration in high risk workers.

It is also quite possible that other factors also play a role in the disease, perhaps in combination with heat stress and dehydration. Exposures to specific agrochemicals or other yet-unknown toxins need further evaluation as possible risk factors related to disease initiation or progression. The roles of infectious agents, NSAIDs, genetic susceptibility, gene-environment interactions and social determinants as contributors to disease onset and progression also need to be clarified.

Social and economic drivers of the disease, including working conditions, unemployment and precarious employment and poverty in general need to be analyzed both in community and workplace studies.

There is a need for standardized studies (including simple prevalence studies) to enable valid comparisons between countries and regions. This is an important step in ascertaining whether the epidemic of CKDu in Central America that we have called MeN is pathophysiologically similar to what is occurring in other parts of the world. Coordinated regional approaches to study prevalence, etiology, and to evaluate interventions are needed to find the causes of this disease and to seek viable solutions the challenges it presents.

Statement of the CENCAM Board and the Scientific Committee of the 2nd International Workshop on Mesoamerican Nephropathy regarding currently known facts about the epidemic

The 2nd International Workshop on the Epidemic of Mesoamerican Nephropathy (MeN) was held in San José, Costa Rica, November 18-20, 2015, three years after the first workshop. A total of 75 experts from 18 countries discussed the evidence regarding possible causes of MeN, pathophysiologic pathways, and similarities and differences with other epidemics of chronic kidney disease unrelated to traditional CKD causes of diabetes and hypertension (CKDu) in Sri Lanka and other parts of the world. The discussion also addressed methods to assess different aspects of the epidemic, ranging from etiologic questions to interventions aimed at prevention. A comprehensive technical report is in preparation, but an interim statement of some key conclusions about MeN is justified considering the urgency of taking action to address this fatal disease.

There was a consensus that MeN has predominantly an occupational component. This conclusion is based on multiple studies with various designs by different research groups in several countries. There is growing evidence for a causal role of strenuous work, heat and insufficient rehydration as risk factors in MeN, and progress has been made towards clarify-

Declaración de la Junta del CENCAM y el Comité Científico del 2do Taller Internacional sobre Nefropatía Mesoamericana referente a los hechos actualmente conocidos sobre la epidemia

El 2do Taller Internacional sobre la Epidemia de Nefropatía Mesoamericana (MeN, por su nombre en inglés) fue celebrado en San José, Costa Rica, del 18 al 20 de noviembre del 2015, tres años después de realizar el primer taller. Un total de 75 expertos de 18 países discutieron la evidencia sobre las posibles causas de la MeN, sus secuencias fisiopatológicas, y las similitudes y diferencias con otras epidemias de enfermedad renal crónica no relacionada con las causas de tradicionales de diabetes e hipertensión (ERCu) en Sri Lanka y otras partes del mundo. La discusión también incluyó los métodos para evaluar diferentes aspectos de la epidemia, que abarcaron desde preguntas sobre su etiología hasta las intervenciones dirigidas a su prevención. Actualmente estamos preparando un informe técnico completo, pero considerando la urgencia de tomar medidas para hacer frente a esta enfermedad mortal, se justifica divulgar esta declaración inicial con algunas de las conclusiones claves sobre la MeN.

Hubo consenso en que la Nefropatía Mesoamericana tiene un componente predominantemente ocupacional. Dicha conclusión se basa en los múltiples estudios con variedad de diseños realizados por múltiples grupos de investigación y en diferentes países. Hay evidencia creciente sobre el papel causal del trabajo extenuante, el calor y la rehidratación insuficiente como factores de riesgo en la MeN; y se ha progresado en la clarificación de las vías fisiopatológicas del estrés por calor que conduce a la enfermedad renal crónica. Por ende, se justifica realizar estudios de intervención para reducir el estrés por calor y la deshidratación en trabajadores de alto riesgo y, de hecho, ya se inició un importante esing pathophysiological pathways for heat stress leading to chronic kidney disease. Intervention studies to reduce heat stress and dehydration in high risk workers are warranted, and one major study has been initiated. However, it is quite possible that other factors also play a role, perhaps in combination with heat stress and dehydration. Exposures to specific agrochemicals or other yet-unknown toxins need further evaluation as possible risk factors related to disease initiation or progression. Based on studies conducted to date, no evidence exists for exposure to heavy metals or alcohol as sole or important risk factors for MeN. The roles of infectious agents, NSAIDs, genetic susceptibility, gene-environment interactions and social determinants as contributors to disease onset and progression also need to be clarified.

Social and economic drivers of the disease, including working conditions, unemployment and precarious employment, and poverty in general need to be analyzed both in community and workplace studies. The need for alternative, improved work environments, particularly concerning heat conditions and agrochemical exposures, was underlined as was the need for improved healthcare for the victims of the epidemic.

Coordinated regional approaches to study prevalence, etiology, and to evaluate interventions were given high priority. Emphasis was also given to a global focus on CKDu, for understanding of the similarities and differences of CKDu epidemics in different geographic areas. In particular, there is a need for standardized studies (including simple prevalence studies) to enable valid comparisons between countries and regions. This is an important step in ascertaining whether the epidemic of CKDu in Central America that we have called MeN is pathophysiologically similar to what is occurring in other parts of the world. In turn, a better understanding of the extent to which CKDu is occurring in multiple locations would provide important information regarding the likely causes of this fatal disease.

tudio al respecto. Sin embargo, se considera que hay otros factores que también pueden jugar un papel importante, posiblemente en combinación con el estrés por calor y la deshidratación. La exposición a algunos agroquímicos específicos o a otros agentes tóxicos aún desconocidos requieren ser evaluados como posibles factores de riesgo relacionados con el origen o la evolución de la enfermedad. Con base en los estudios realizados a la fecha, no existe evidencia sobre la exposición a metales pesados o alcohol como factor único o como factores de riesgo importantes para la MeN. Además, se debe clarificar el papel de los agentes infecciosos, los anti-inflamatorios no esteroideos AINEs, la susceptibilidad genética, las interacciones genético-ambientales y los determinantes sociales, como factores contribuyentes para la aparición y la evolución de la enfermedad.

Se deben analizar los factores sociales y económicos que promueven la enfermedad, incluyendo las condiciones de trabajo, el desempleo, el empleo precario y la pobreza en general, a través de estudios tanto comunitarios como en lugares de trabajo. Se destacó la necesidad de proveer entornos de trabajo alternativos y mejorados, particularmente en ambientes con condiciones de altas temperaturas y exposición a agroquímicos, así como como la necesidad para mejorar la atención de la salud de las víctimas de la epidemia.

Se dio alta prioridad a los enfoques regionales coordinados para estudiar la prevalencia y la etiología, y para evaluar las intervenciones. También se dio un gran énfasis al enfoque global de la ERCu, para entender las similitudes y diferencias de la epidemia de ERCu en diferentes áreas geográficas. En particular, es necesario realizar estudios estandarizados (incluyendo estudios sencillos de prevalencia) que permitan hacer comparaciones válidas entre países y regiones. Este es un paso muy importante para determinar si la epidemia de ERCu en Centroamérica que hemos llamado MeN, es similar a las que están ocurriendo en otras partes del mundo. A su vez, el tener un mejor entendimiento sobre el grado en que la ERCu está ocurriendo en múltiples localizaciones, podría proporcionar información importante relacionada con las causas probables de esta enfermedad mortal.

Dr. Norman Solórzano Alfaro, Vice-Rector de Docencia en representación del Sr. Rector el Señor Rector de la Universidad Nacional Dr. Alberto Salom Echeverría.
Dra. Catharina Wesseling, Presidenta del CENCAM.
Máster Pelayo Castro Zuzuarregui, embajador para Centroamérica de la Unión Europa.
Dr. Mario Cruz, en representación de la Dra. Lilian Renau de la Organización Panamericana de la Salud.
Dra. Aurora Aragón, en representación de la Máster Marianela Rojas Garbanzo, Coordinadora Regional de SALTRA.

OPENING REMARKS

Palabras del Excelentísimo Pelayo Castro Zuzuarregui
Embajador, Jefe de Delegación de la Unión Europea para Costa Rica.

Dra. Aurora Aragón Benavidez, Representación Coordinadora Regional SALTRA
Dra. Catharina Wesseling, Presidenta Consorcio para la epidemia de la Nefropatía en México y Centro América (CENCAM)
Dra. Lilliam Renau-Vernon, Representante OPS en Costa Rica
Dr. Norman Solórzano Alfaro, Representación Rectoría Universidad Nacional

Les agradezco que me permitan acompañarles en la apertura de un taller como éste en el que participan 79 investigadores de 18 países. Ustedes son los verdaderos y únicos protagonistas.

Hay quienes sostienen que el trabajo de un embajador o un diplomático es ser capaz de hablar de casi todo sin saber de casi nada. Yo prefiero saltarme el protocolo pues en mi caso y en esta ocasión particular sería muy osado por mi parte, sin duda improcedente, intentar decir algo inteligente en materia de nefropatías o nefrología. Les provocaría una piedra en el riñón. Así es que les ahorraré ese atrevimiento y me limitaré a explicarles por qué yo, por qué la Unión Europea, está hoy aquí.

Lo haré compartiendo 3 mensajes muy sencillos.

El primer mensaje
es COOPERACION

La bandera de la UE está hoy aquí porque existe una enfermedad renal crónica de etiología que ustedes están tratando de determinar y que está devastando vidas de trabajadores y sus familias en múltiples rincones de Centroamérica. Ésta es una enfermedad silenciosa que satura los sistemas de salud y provoca muertes prematuras, tragedias personales, pero también una tragedia social. Esa enfermedad necesita ayuda. Esa enfermedad necesita cooperación internacional. Les necesita a ustedes. Por eso la UE está hoy aquí.

La UE ayuda a través de SALTRA en esta y en otras actividades de otros componentes del programa. En el año 2011 la UE se unió a SALTRA (en su Fase II) apoyando con €1.161.886 la "Acción para la incorporación de los principios de desarrollo sostenible en la gestión de salud ambiental y laboral desde las universidades centroamericanas", de la mano de la Universidad Nacional de Costa Rica, lo que le ha permitido a SALTRA compartir experiencias y trasladar sus logros de salud ocupacional de la Fase I al área de salud ambiental.

Se trata, y quiero subrayarlo, de cooperación regional. Y para nosotros tiene un valor añadido fundamental. Creemos en ella. Es nuestra seña de identidad. La UE tiene un Acuerdo de Asociación con América Central – el único entre 2 regiones de esta naturaleza en el mundo – y ha reforzado su cooperación regional con Centroamérica. Nuestra política de apoyo a la región sigue siendo un compromiso a largo plazo ya que la UE quiere seguir siendo un socio de referencia en la región Centroamericana: unos 120 millones de euros están ya previstos para la cooperación regional durante el periodo 2014-2020.

El segundo mensaje es un mensaje social. La salud ocupacional y ambiental es uno de los focos fundamentales del desarrollo sostenible. Y es también una seña de identidad europea. Por eso esta la UE hoy aquí. Yo todavía lo llamo modelo social europeo, porque creo en él. Porque creo que Europa debe seguir siendo sinónimo de liderazgo en educación y sanidad, en políticas sociales, asistencia sanitaria universal, investigación científica y cooperación internacional. La OIT considera que cada año 2.3 millones de personas mueren por accidentes o enfermedades relacionadas con el trabajo. Aparte de las consecuencias dramáticas para sus familias, en términos económicos, significa cada año una pérdida del 4% de crecimiento del PIB mundial. Por eso esté la UE hoy aquí.

Si lo resumimos de manera muy resumida, los contribuyentes europeos están financiando esta actividad para vencer a una enfermedad lejana y generar salud y esperanza al otro lado del océano. Y lo están haciendo con un método muy comunitario y muy europeo: trabajar conjuntamente, aprendiendo de los demás, compartiendo experiencias, apoyándonos en la ciencia, uniendo a investigadores de 19 países por encima de fronteras.

El **tercer mensaje tiene que ver con el riñón.** No soy un experto como ustedes. Por eso me disculparán que diga que he leído que los riñones limpian el cuerpo de residuos, y que metafóricamente, algunos creen que limpian el cuerpo de toxinas e ideas negativas. Al riñón se le asocia con la purificación pero también con la concentración de emociones de estrés, miedo, ansiedad, incertidumbre, terror, etc. Llevando la metáfora un poco más lejos, y por deformación profesional, podríamos decir que el riñón del mundo está enfermo. Sufre una nefropatía muy grave. Me perdonarán que tenga muy presente los atentados de París, que se han clavado en el corazón de la familia europea. Pero no sólo los de Paris. Los atentados de Beirut, de Túnez, del Sinaí, Nigeria, Ankara y tantos otros rincones del planeta. Fueron ataques contra la humanidad. Contra todos nosotros.

El riñón del mundo está enfermo. Pero el taller que hoy se inaugura, ver a tantas nacionalidades juntas, saltando fronteras, cooperando para enfrentarse a una enfermedad es un pequeño acto de esperanza. El riñón del mundo se puede curar. Va a ser difícil. Y para lograrlo hace falta una Europa unida y mucha cooperación internacional. No es solamente una cuestión de diplomáticos, ni mucho menos. Es una cuestión que nos interpela a todos, todos los días. También hoy aquí.

Ustedes están hoy aquí para colaborar, para aportar y trabajar duro, para dejarse los riñones y cambiar la vida de los miles de personas afectadas en este momento por la epidemia de la nefropatía renal crónica, para descubrir su causa. Para generar esperanza, para evitar en definitiva que las víctimas de esta grave enfermedad sigan creciendo en Centroamérica, Asia y posiblemente otras partes del mundo.

Para finalizar, quisiera desearles los mejores éxitos durante el desarrollo de este evento.

MESSAGE OF WELCOME

Palabras de Marianela Rojas Garbanzo
Directora del Programa Salud, Trabajo y Ambiente, Costa Rica

Excelentísimo Señor Pelayo Castro Zuzuarregui, Embajador para Centroamérica de la UE
Dra. Catharina Wesseling, Presidente de CENCAM y fundadora del programa SALTRA
Dr. Cruz, OPS
Dr. Norman Solórzano, Representante de la Rectoría de la UNA (Vice-Rector de Docencia)

En nombre de Marianela Rojas, Directora del Programa Salud, Trabajo y Ambiente, coordinado desde el IRET de la Universidad Nacional, y de mis colegas coordinadores nacionales de SALTRA desde Guatemala hasta Panamá, les damos la más cordial bienvenida a Costa Rica y al II Taller Internacional de Investigación sobre la Nefropatía Mesoamericana.

De nuevo nos damos cita más de 75 profesionales y científicos de 15 países, comprometidos no sólo con seguir esclareciendo el enigma de la enfermedad renal crónica de causa desconocida, o Nefropatía Mesoamericana a como la hemos llamado, si no que también con la comunicación, la difusión y la incidencia.

Quisiera destacar la presencia del Dr. Christer Hogstedt y la Dra. Catharina Wesseling, cofundadores del Programa SALTRA, quienes han trabajado incansablemente en la región centroamericana para atender este asunto de importancia regional.

El Programa SALTRA, para quienes no lo conocen, es un programa que fue creado hace más de 12 años para avanzar en el desarrollo de la salud de los trabajadores centroamericanos, desde las universidades nacionales de los países centroamericanos. Hoy en día el programa, gracias al trabajo de los colaboradores y el apoyo decidido de sus fundadores y contrapartes estratégicas, ha logrado enraizarse en cada uno de los países y contribuir con investigación, diferentes modelos de educación, herramientas para el registro y la vigilancia de la salud ocupacional y sobre todo, en la promoción de redes y alianzas con diferentes actores en los países centroamericanos. Es precisamente, debido a la misión de SALTRA, que desde el 2003, bajo la Dirección de la Dra. Catharina Wesseling colocó en su agenda de trabajo, acciones para la investigación de la Enfermedad Renal dando lugar al primer encuentro Centroamericano con nefrólogos, y epidemiólogos que por referencia habían escrito o tenían alguna experiencia que contar en torno a la enfermedad. De ahí surgieron dos investigaciones hermanas en Nicaragua y El Salvador, y en 2009 un segundo encuentro con nuevos actores en coordinación esa vez con el representante de la de la Sociedad Latinoamericana de Nefrología e Hipertensión Dr. Ricardo Correa Rotter hasta dar lugar al primer taller de CENCAM.

Hoy, estamos aquí la mayoría de las personas que estuvimos en el Taller anterior, con nuestros aliados y colaboradores como la OPS que declaró esta epidemia como un problema de salud pública, y también hay gente nueva que se ha ido sumando a esta iniciativa con ideas, investigaciones, y acciones.

A como lo veremos durante el taller, a pesar que hemos avanzado sustancialmente en la investigación de esta enfermedad, algunas causas y mecanismos que hacen que esta enfermedad progrese tan rápidamente, siguen siendo desconocidos, y que seguramente reafirmaremos la necesidad de desarrollar acciones que permitan reducir las consecuencias trágicas de esta enfermedad.

SALTRA como programa académico tiene el compromiso de continuar atendiendo este problema y apoyar a los gobiernos para buscar soluciones y la definición de políticas en salud, sociales y económicas. Sin embargo, ante la complejidad de este enigma, siguen siendo absolutamente necesarias las alianzas internacionales de los científicos y expertos que ya son parte, y de nuevos actores de distintas disciplinas de otras partes del mundo.

Exactamente 3 años despues del primer taller MeN, SALTRA continua apoyando, ahora junto a CENCAM, la convocatoria de socios y aliados para continuar evaluando el problema y buscar la dirección hacia donde enfocar nuevos esfuerzos para llegar a soluciones eficaces. Los que estamos aquí sabemos que esta enfermedad, no espera nuestros resultados y que sigue afectando a muchos trabajadores quienes sin tratamiento fallecen a edades tempranas y que la atención médica sigue desbordando la capacidad de los sistemas de salud en varios países de la región. Es también la misión de SALTRA mantener el apoyo a través de sus representantes en los países para que se siga investigando problemas sociales y proponer soluciones.

Finalmente quisiera enfatizar el objetivo del taller. Estamos hoy aquí con el propósito de colaborar para lograr una diferencia para los miles de personas afectadas en este momento por la epidemia de enfermedad renal crónica de causa desconocida, para todas aquellas personas que caerán víctimas de esta grave enfermedad en el futuro, y también pensando en los miles de trabajadores ya fallecidos, en Centroamérica, y posiblemente otras partes del mundo. Tenemos una oportunidad única de revisar, reflexionar y planificar como grupo, de integrar eficiencia y eficacia en los futuros planes de investigación y de acción.

Una vez más en nombre de mis colegas de SALTRA y particularmente de Marianela Rojas, les agradecemos su presencia y les decimos que confiamos que juntos aprovecharemos esta oportunidad con madurez y sabiduría.

Gracias por venir y estar aquí durante estos tres días. Que sean todos muy bienvenidos.

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PROLOGUE

This report is the result of the Second International Workshop of Mesoamerican Nephropathy (MeN 2015) held November 18-20, 2015, which was part of an increasingly collaborative effort of researchers and other actors to coordinate efforts to understand and find solutions for chronic kidney disease of unknown etiology (CKDu) in Mesoamerica and other parts of the world.

History

Workers in Mesoamerica have been aware of MeN for more than 20 years and only a few researchers became aware and convinced of the need to research this disease before the year 2000. In November 2005, recognizing the need for collaboration and a coordinated vision for research, SALTRA[1] convened a Central American workshop in León, Nicaragua about CKD (http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=90&Itemid=260).

Over the next 5 years, researchers from Central America, North America and Sweden started to characterize the unique chronic kidney disease (CKD) that was occurring and explore hypotheses about its causes. In 2010, SALTRA together with the Autonomoous University of Mexico (UNAM) to hold a second workshop – this time with aimed at increasing collaboration in the region and at bridging the gap between

1. In 2005 SALTRA was the Program on Work and Health, Phase I, a Central American-Swedish collaborative university-based research and action program to improve occupational health in the region. Phase I was funded by Sida and received also US and other international support.

the disciplines involved ranging from occupational health to epidemiology to nephrology. This led to the creation of RERCEM, the Network for the Study of Mesoamerican Nephropathy

(http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=90&Itemid=260).

MeN 2012 Workshop

The epidemic continued to advance and suffering of patients and their families along with the increasing inability of the healthcare systems to respond adequately, made it clear that broader international collaborations and funding were needed to accelerate research. As researchers in other part of the world starting becoming aware of the problem, some offered to become involved. In 2012, SALTRA convened an International Organizing Committee and set a date for the First International Workshop of Mesoamerican Nephropathy (MeN 2012). For three days in Novembers 2012, a total of 51 researchers from 15 different countries set out to answer the questions, "What do we know?" "What do we *need* to know?" and to come to consensus on 1) A prioritized research agenda and 2) ways to collaborate, improve coherence between research initiatives and use scarce resources more efficiently. These were lofty goals for the 51 participants, especially given the historic tension and differences between research groups and other actors in the region at that time. It must be said that the participants of the 2012 workshop knew the task that they were undertaking and believed in its importance – so much so that each participant paid his or her own expenses to attend the workshop.

The participants in MeN 2012 held this meeting in a global context in which the very *existence* of Mesoamerican Nephropathy[2]. As such, one of the most important achievements of the MeN 2012 was the signing of a statement(http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=114) including the declaration that "...that there is sufficient proof of a chronic kidney disease of undetermined origin (MeNu) affecting Mesoamerica..."

The Statement goes on to say that "Global and local interdisciplinary action and research are essential to address this urgent and tragic public health problem. As such, we offer our support to governments to aid them in recognizing the disease in Central America and to collaborate with local researchers and multi-sector actors to:

1. Address this issue by pooling resources and using existing scientific evidence,

2. Prevent premature deaths in the most affected populations by intervening where possible."

The participants also decided to form a research consortium, which came to be called CENCAM (Consortium on the Epidemic of Nephropathy in Central America and Mexico), to facilitate collaboration between researchers working on the disease.

MeN 2015

The work of CENCAM as well as the scientific and political developments between the first and second workshops are detailed in this report, (see *"What has happened since the 1st Mesoamerican Nephropathy Workshop?"*). Simply put, the scientific and political contexts changed dramatically between 2012 and 2015. It is difficult to overstate the importance of the progress made in these three years in the scientific and political arenas. Nonetheless, it is also true that the situation for the individuals affected by this disease and their families has <u>*not*</u> changed dramatically. This was the important reality guiding the participants of the 2015 workshop and will remain the reality that should guide our current efforts.

The participants of MeN 2015 included 80 researchers from 19 different countries and many different specialties. Their names and institutions can be found at the end of this report.

Objectives of MeN 2015

The goals of the workshop were to:

1. Update progress in understanding the epidemic and on the research questions identified at First International Workshop.

2. Share ongoing studies in the region and identify current knowledge gaps.

2. See note below regarding names for the disease.

3. Articulate key hypotheses and strength of evidence to date with a view to focus future research on the most promising hypotheses.
4. Promote and establish new relationships and collaboration among researchers and clinicians.
5. Identify data and data sources to inform the public, clinicians, labor market partners, and policy makers in understanding the evidence base of interventions and solutions for the prevention and treatment of CKDnT.
6. Strengthen the communication and support structure for researchers in the region
7. Publish proceedings, peer-review papers summarizing progress and research gaps and host in-person CENCAM meeting.

Simply put, we aimed to answer the following questions, updating the answers we documented in the 2012 workshop:
1. What do we know?
2. What do we need to know and understand?
3. How can we advance?
4. What are the top priority research initiatives?

MeN 2015 Methods and Outcomes

What do we know?
What do we need to know and understand?

The 2015 MeN workshop was designed to obtain maximum participation from the participants. Oral presentations were invited from researchers prior to the workshop with the aim to summarize recent research outcomes and update data relevant to etiologic hypotheses disease. Their written submissions were reviewed by the Scientific Sub-Committee, revised accordingly. They were distributed to all workshop participants prior to the workshop and presented orally during the workshop. Following the workshop, authors were asked to update their papers to reflect discussions and new data presented at the workshop and re-submit them to the Scientific Sub-Committee for final review and acceptance for this report. Posters were also solicited from any participant wishing to inform about recent and ongoing work. All posters were presented orally in a session during the workshop. The abstracts are included in this report.

How can we advance?

The workshop also included working groups led by 2-3 researchers familiar with the designated topics. Each workshop attendee participated in two working groups and the summaries from each presented orally and discussed in a plenary session with all participants. The written summaries were updated by the working group leaders to reflect the plenary discussion and submitted for review by the Scientific Sub-Committee before being accepted for inclusion in this report.

What are the top priority research initiatives?

The final part of the workshop focused on setting research priorities and including a summary of the proposals set forth by working groups and a summary by five members of the Organizing Committee. Suggestions for moving forward can be found in each working group summary and a summary of the consensuses reached during the workshop can be found in the Statement by the Board available online
(http://repositorio.una.ac.cr/bitstream/handle/11056/12869/Board%20Statement%20MeN.pdf?sequence=1) as well as in this report.

This report

It is our hope that this report will serve as a useful tool for researchers interested in collaborating to increase the efficiency and effectiveness of their work and by policy makers seeking to address chronic kidney disease of unknown origin. We are increasingly aware of similar epidemics in other parts of the world and hope to contribute to the worldwide efforts looking for causes and solutions.

Thanks to a grant from the National Institute of Environmental and Occupational Health Sciences (NIEHS) in the United States awarded jointly to Boston University and the Universidad

Nacional in Heredia, we were able to provide simultaneous English-Spanish translation during the workshop and thanks to a generous offer from the National Institute for Occupational Safety and Health (NIOSH) in the United States, we are able to translate the content of this report to Spanish. We hope that this will add to the usability of this report.

Heredia, May 15, 2016

The Organizing Committee

Ricardo Correa-Rotter
Jennifer Crowe (Secretary)*
Ramón García-Trabanino
Marvin González Quiroz
Carolina Guzmán Quilo
Christer Hogstedt*
Kristina Jakobsson*
Rebecka Lucas
Madeleine Scammell
Agnes Soares
David Wegman*
Ineke Wesseling (Chair)*

*Denotes Scientific Committee Members.

Notes

- The workshop title used the term 'Mesoamerican Nephropathy'. The acronym 'MeN' (originally MEN with the "e" refering to "endemic" or "epidemic", was used before the 2012 workshop. However, it was pointed out during the 2012 workshop, that 'MeN' is an acronym that might appear to exclude attention to women as victims of the disease and that another name should be proposed. Since 2012, multiple names have been coined to refer to the disease. CKDu (chronic kidney disease of unknown origin) was used during the 2012 workshop and CKDnT (chronic kidney disease of non-traditional causes) tends to be used by PAHO and Central American governments. In Sri Lanka, the name Chronic Interstitial Nephritis in Agricultural Communities (CINAC) is used. The choice of the most appropriate name for the disease was discussed at length in the General Assembly in November 2015 and different opinions remain about the most appropriate name. This report generally uses CKDu to refer to the disease worldwide and MeN to refer to CKDu occurring in the Mesoamerican Region. However, the term used by each author was respected in this report.
- Throughout the document there is an inconsistent use of the terms Mesoamerica and Central America. There are different definitions for delimitations regarding Middle America, depending on whether the focus is geographic, geological, historical, cultural, political or economic. Panama (the most southern country), Belize (the only ex-British colony of the isthmus), or the south of Mexico (Mexico is considered part of North-America) may be included or excluded. We must keep in mind that for the study of the MeN epidemic, we target from south to north: Panama, Costa Rica, Nicaragua, El Salvador, Honduras, Belize, Guatemala, and the south of Mexico.
- We are grateful for the work done by the authors contributing the pre-workshop papers, the rapporteurs and

facilitators from all the discussion groups and the abstract authors. We are also deeply grateful for the work done by those who worked behind the scenes to help assure the success of the workshop and the publication and translation of this document (see Acknowledgements).

- The contents of all papers and posters remain the opinion and responsibility of the authors and, unlike the summaries of rotating table discussions and working group discussions, are not to be considered consented workshop conclusions.
- The content of the publication is the responsibility of the authors and the SALTRA program. The content does not necessarily reflect the opinion of the European Union, which provided funding for SALTRA at the time the workshop was held nor does it represent the opinions of NIEHS which provided funding for layout design or NIOSH which generously translated the report.

2ND INTERNATIONAL WORKSHOP ON MESOAMERICAN NEPHROPATHY

November 18-20, 2015

Theme: What do we know?

Advances in knowledge of CKDu

What has happened since the 1st Mesoamerican Nephropathy Workshop?

The Organizing Committee of the 1st MeN workshop in 2012:
Catharina Wesseling, Chair CENCAM; Karolinska Institutet, Stockholm, Sweden
Jennifer Crowe, SALTRA, IRET-UNA, Heredia, Costa Rica
Christer Hogstedt, Karolinska Institutet, Stockholm, Sweden
Kristina Jakobsson, University of Gothenburg; University of Lund, Sweden
Rebekah Lucas, University of Birmingham, UK
David H. Wegman, University of Massachusetts Lowell, USA

Background: 1st MeN workshop

Exactly three years ago, nearing the end of 2012, the Central American Program on Work, Environment and Health (SALTRA) organized the *1st International Research Workshop on the Mesoamerican Epidemic Nephropathy (MeN)* (Figure 1). Fifty-five researchers from North, Central and South America, Europe and Sri Lanka conducted an in-depth review of the existing knowledge on the epidemic. The workshop identified knowledge gaps and knowledge that must be generated to clarify the causes and propose prevention and mitigation measures. At the end of the workshop, we reached consensus on concepts and priorities for research and action.

The workshop concluded that MeN was well-identified in certain parts of Nicaragua, El Salvador and Costa Rica, but not universally observed throughout these countries, and the absence of adequate prevalence studies in most of Mesoamerica was a recognized concern. It was not clear if the epidemics observed in Sri Lanka and India resulted from the same disease or were caused by the same factors as in Mesoamerica. The cause of MeN remained uncertain; however, the leading hypothesis was that the disease was linked to repeated episodes of occupational heat stress and water/solute loss, possibly in combination with other potential risk factor(s) such as use of nonsteroidal anti-inflammatory drug and other nephrotoxic medications, inorganic arsenic, leptospirosis, or pesticides. Although genetic susceptibility was discussed as a theoretically plausible risk factor, no studies exploring genetics were reported. It was emphasized that social factors, including work organization, migration patterns, and other local and macro socioeconomic drivers strongly influence disease occurrence.

To maximize future research, the workshop recommended to establish case definitions for clinical purposes and epidemiologic research,

Figure 1. Participants in the 1st International Research Workshop on the Mesoamerican Epidemic Nephropathy (MeN).

the development and validation of biomarkers of early and late disease, and methods for correct measurements of risk factors including a common questionnaire. The workshop also recommended more biopsy and prevalence studies and, despite their high costs, prospective cohort studies in occupational groups or contrasting communities. Intervention studies to reduce heat stress and improve hydration with adequate electrolyte replacement were considered necessary. Finally, the workshop concluded with the establishment of a research consortium, which was later named the Consortium on the Epidemic of Nephropathy in Central America and Mexico (CENCAM), to facilitate collaboration between researchers working on the disease.

What has happened since?

SCIENTIFIC ADVANCES

In the past three years, publications directly or indirectly related to the Mesoamerican nephropathy (MeN) have been appearing at an increasingly rapid pace, and to a somewhat lesser degree, in relation to similar epidemics in other geographical regions. Presentations about MeN and CENCAM have been given at major scientific conferences. The CENCAM Board has made a provisional list of peer reviewed publications starting from January 2013, which includes articles related to MeN or CKD in Mesoamerica and to CKDu or CKDnT in other regions, aiming for periodic updating. It is clear that the current number of research groups and individual researchers investigating topics related to MeN is considerably larger than at the time of the MeN workshop in 2012.

The program of the 2015 workshop includes presentations about most topics that have been proposed as potential causes or co-factors, and ongoing research by several research groups in Mesoamerica and Sri Lanka. For the purpose of this overview, it suffices to note that studies in Central America have demonstrated the occupational nature of the disease, albeit possibly with other contributing causes. Important research results have been obtained quantifying the strenuous nature of work, the very hot climatic conditions, and potential pathophysiological pathways leading to CKD. Furthermore, animal experimental data has challenged the classical dogma that dehydration does not cause CKD. The first intervention study to prevent heat stress and dehydration among sugarcane cutters began in November 2014. Studies of occupational cohorts in different worker populations and at least one community cohort are underway. The hypothesis that pesticides are a main cause of MeN has decreased in urgency, but has not been abandoned since the etiologic nature of pesticides has not been exhaustively investigated in Mesoamerica. Genetic susceptibility and leptospirosis hypotheses are at an initial stage of exploration. Other topics that have not been addressed sufficiently include the overall burden of MeN, clinical aspects of accessibility, and success rate of treatments and survival of MeN patients. Gender differences need to be better understood with remaining uncertainties as to why rates among women have increased in affected areas, albeit in much lesser degree than among men. Of note, there is increasing interest in exploring the similarities and differences between MeN and similar epidemics, especially in Sri Lanka and India. In these Asian countries, pesticides continue to be an important hypothesis and research topic, whereas no investigations regarding heat stress and dehydration have been published.

INCREASED PUBLICITY OF MeN

The international awareness of MeN has increased also thanks to immense media publicity. During the last three years, articles about the MeN epidemic and related scientific, social and political issues have been published by scientific journalists in Science, The Lancet and the British Medical Journal. Press articles and radio programs have appeared in major news media including the New York Times, Center for Public Integrity, US Public Broadcasting System (PBS), National Geographic, The Guardian, as well as many local newspapers and radio and television programs.

POLITICAL DEVELOPMENTS IN MESOAMERICA

After the 1st MeN workshop in 2012, the already long-existing awareness and concerns of most governments of Central American countries and regional organizations translated into specific resolutions and actions, which were outlined in detail in one of the introductory presentations at the 2015 workshop (see *"Interventions, regulations and response of health care systems in Central America"* in this report). Several key political meetings have yielded statements highlighting Mesoamerican nephropathy as a priority public health problem and urging governments to act, specifically the San Salvador Declaration of the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA) in April 2013, and Resolution CD52/8 of the Pan American Health Organization (PAHO) Assembly in October 2013. In addition, the Latin American Society of Nephrology and Hypertension (SLANH), PAHO and the US Center of Disease Control (CDC) organized a workshop in Guatemala in 2014 to develop a clinical definition for the chronic kidney disease epidemic in Central America. Specific governmental actions include the efforts of the Salvadorian Ministry of Health to ban nephrotoxic and other hazardous pesticides in 2013; the establishment of interinstitutional committees on CKD in Guatemala in 2013 and Costa Rica in 2014; a Decree of the Costa Rican government to regulate occupational heat exposure in 2015; and a PAHO meeting in Nicaragua to develop regional strategies to address the epidemic.

At the start of this past three-year period, social and economic issues related to Mesoamerican nephropathy were highly sensitive and in some parts of the region resulted in social unrest. Research into the etiology of MeN has struck ethical and political chords, in some cases negatively affecting researchers. There have been accusations of conflicts of interest due to industry funding (both sugarcane and pesticides) and industry has also interfered with data interpretation and publication as well as plain research obstruction. Some of these issues have considerably improved in the last year and a half, partly thanks to the increasing political awareness of regional organizations and national governments, pressure from affected parties, more interchange between research groups (especially through CENCAM), and in general an improved collaborative attitude that results from increased research capacity. Also the CENCAM Board has contributed to a more peaceful research environment by following the recommendations of a subcommittee established to provide guidance on how CENCAM can help solve politically difficult research situations in Central America. Of note is the general increased willingness among sugarcane companies to respond to the epidemic through preventive actions. The earlier mentioned heat stress and dehydration intervention study in El Salvador is conducted in full collaboration and harmony with the second largest mill in the country. Also other sugar-related companies in Central America are increasingly opening up to implementation of heat stress prevention measures.

Despite these positive developments, significant gaps in our understanding of the mechanisms underlying the disease and the potential influence of different risk factors still remain. The number of individuals suffering from MeN continues to rise, and will continue to do so until appropriate interventions can be directed to address major risk factors and related safeguards are implemented.

CENCAM development

CENCAM's mission was defined as contributing to knowledge generation and promoting and facilitating activities and policies to reduce CKDu occurrence in Central America and Mexico. The inaugural board was elected in July 2013 and CENCAM has slowly established itself as a solid and active organization. The board holds regular meetings (about 6 per year). The secretariat is run by the Central American Program on Work and Health of the Universidad Nacional (SALTRA/UNA) in Costa Rica. The secretariat distributes the minutes of board meetings and regular communications about relevant topics to CENCAM members and a listserve allows for direct communication between all members. CENCAM has two websites. Membership increased from the initial 55 members from 15 countries in November 2012 to 103 members from 22 countries in October 2015. SALTRA and CENCAM jointly organized the 2nd International Workshop on Mesoamerican Nephropathy. The first General Member Assembly was held on Friday November 20, 2015, with the presentation of a detailed report.

Notable today is that researchers know each other better than before, often as a result of CENCAM. Increasing overlap of research groups on different publications can be seen as an indicator for evolving collaboration between groups. Several research collaborations developed within CENCAM, one example being a grant given by the International Society of Nephrology (ISN) to compare biopsies between MeN and Sri Lanka CKDu patients, with participation of CENCAM members from Central American, Sweden and Sri Lanka.

In summary, in these three years, we have achieved increased knowledge, a much larger international awareness, and a better research environment with increased collaboration. However, there is still much to learn in theory and in practice to prevent MeN, and researchers need to continue expanding collaborations and bringing together their expertise.

In which countries and occupations has CKDnT been reported in excess and how well has it been studied where there are no reports?

Kristina Jakobsson, Department of Occupational and Environmental Medicine
Gothenburg University, Sweden.

What do we know?

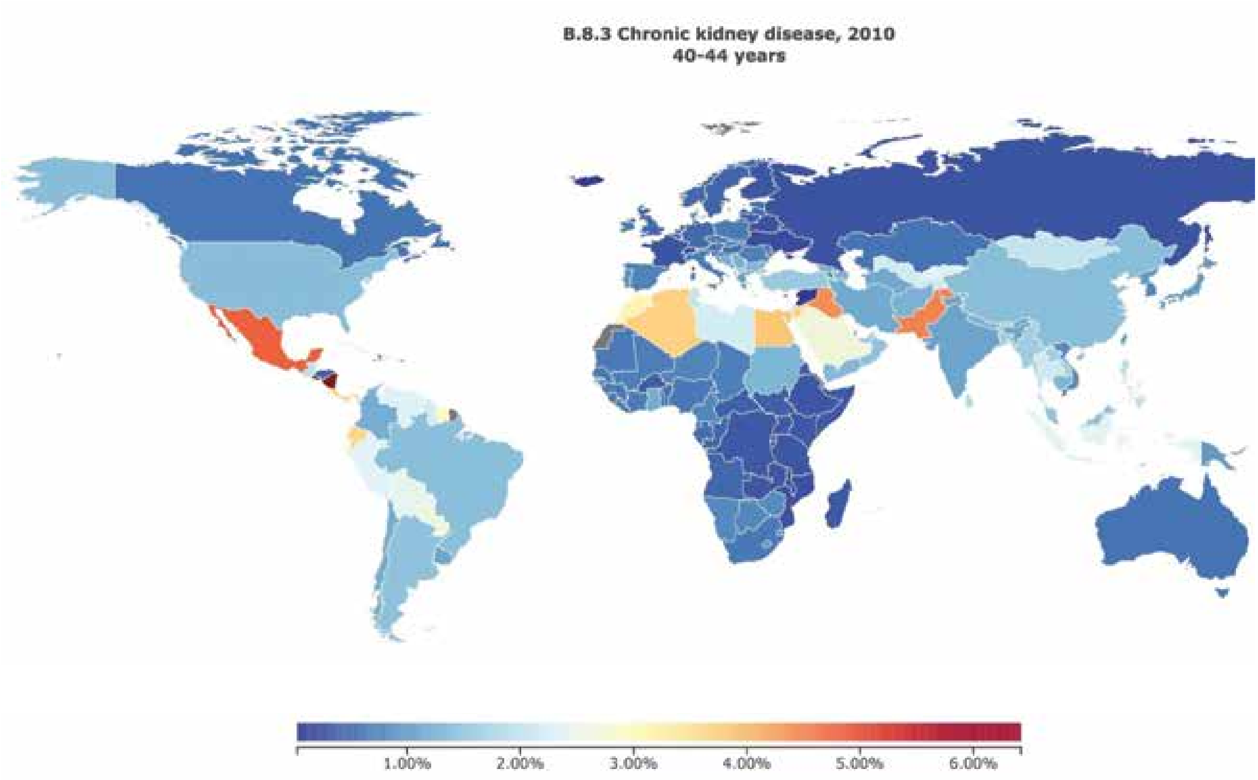
Sources of information and their limitations

The **WHO mortality registry** is available on-line (http://www.who.int/healthinfo/mortality_data/en/), with easy-to use modules for data retrieval. The problems with mortality data quality are well known, but the most obvious limitation is the lack of data. Many countries that have mortality registries have not reported to the database. The same limitation holds for population statistics.

The **WHO Global burden of disease project** has assembled data on non-communicable diseases including CKD from many available sources. These data are available on-line, with convenient modules for mortality, years of life lost (YLL) and disability-adjusted life year (DALY) mapping and time-trends.(1) Much of this information is based on scarce data, modeling and assumptions and has to be used with great caution. Moreover, data on a national scale will not capture important regional variations.

As seen in the map (Figure 1), Mexico, El Salvador and Nicaragua are hot-spots. These countries have also marked increases in YLLs (years of life lost due to premature mortality) between 1990

Figure 1. Mapping of CKD mortality in males, aged 40-44, 2010. Accessed from www.healthdata.org/gbd



and 2013. Several countries in North Africa are also identified as hotspots, but here YLLs have not increased during the observation period. Also, Iraq has a high CKD mortality without YLL increase between 1990 and 2013. The existing regional endemic in Sri Lanka is apparently not affecting the national rates. Pakistan –a country without a mortality registry- is identified as a distinct hot-spot (see also further below).

End-stage renal disease (ESRD) and renal replacement therapy (RRT) registries are available in some, but still too few countries. The United States Renal Data System (USRDS) collects data each year for international comparisons.(2) Countries report incidence and prevalence data according to a standardized format. Reports include, as possible, patient count data for the entire population, by sex (male, female), or by five different age categories (0-19, 20-44, 45-64, 65-74, 75+) for patients new to ESRD during the year. Reports also can include numbers undergoing different types of treatment.

Underlying risk factors (diabetes, hypertension) are reported most commonly as the cause of disease requiring RRT. However, in countries with limited healthcare resources, the patients included in such registries cannot be considered representative of the total diseased population in the catchment areas. Moreover, population age distributions are not comparable between countries. Thus, information from such registries is not informative on the CKDu disease burden, but can give interesting information on differences in the use of RRT between countries, and on diabetes as a risk factor for ESRD.

In 2013, reported rates of the incidence of ESRD varied greatly across 51 countries (Figure 2). Taiwan, Jalisco (Mexico), U.S. and Singapore reported the highest rates of ESRD incidence ranging from 458 to 308 per million population. (3) Below these areas, ESRD incidence rates of nine other countries were reported between 208 (Indonesia) and 286 (Japan) per million population. The lowest ESRD incidence rates were reported in 9 countries between 45 (Bangladesh) and 96 (Scotland). In the remaining countries, incident ESRD rates ranged from 100 to 195 per million population. Since reporting is strongly affected by health care access the incidence rates reported are not indicative of true disease incidence between different countries and regions.

The proportion of ESRD cases where diabetes was listed as the primary cause was available for 46 of the 51 countries or regions. Figure 3 summarizes information available by country for all causes reported to the USRDS for 2013. (4) Approximately half to two-thirds of cases were associated with diabetes in Malaysia, Singapore, Jalisco (Mexico), Hong Kong, New Zealand and Rep. of Korea. At the other extreme, 15 to 20% were reported for Romania, Iceland, Netherlands, and Norway. Belgium and Estonia. In 34 countries incidence rates were reported by sex. All countries reported higher incidence in males than females although the ratio varied between 1.2 in Malaysia to 2.2 in Denmark.

Kidney Disease Data Center. In 2005, the International Society of Nephrology (ISN) established a program aimed at building global capacity for preventing CKD in developing nations. By 2009, more than 25 programs had been established on five continents and had enrolled more than 38,000 subjects. Publications can be found searching for "Screening and Early Evaluation of Kidney disease – SEEK".

In 2007, the ISN funded the establishment of an electronic database (Kidney Disease Data Center [KDDC]) in Bergamo, Italy, to support the collection and analysis of data. An analysis with focus on findings from screening programs in South East Asia was recently published.(5) The investigators report a widely varying prevalence with certain regions experiencing high prevalence of CKDu affecting younger populations in poor communities. Caucasians generally have lower rates than Asians but whether ethnicity or environmental factors explain the differences is not known. Access to health care certainly accounts for some differences that complicate interpretation of CKD patterns. Nonetheless improved health care apparently has resulted in increasing numbers of those receiving RTT.

NGO and media reports are another source of information. An example: In eastern India, certain coastal villages in the Uddanam area

Figure 2. International comparison of incidence of ESRD/million population, 2013 (taken from Volume 2, Chapter 13 accessed at http://www.usrds.org/2015/view/Default.aspx)

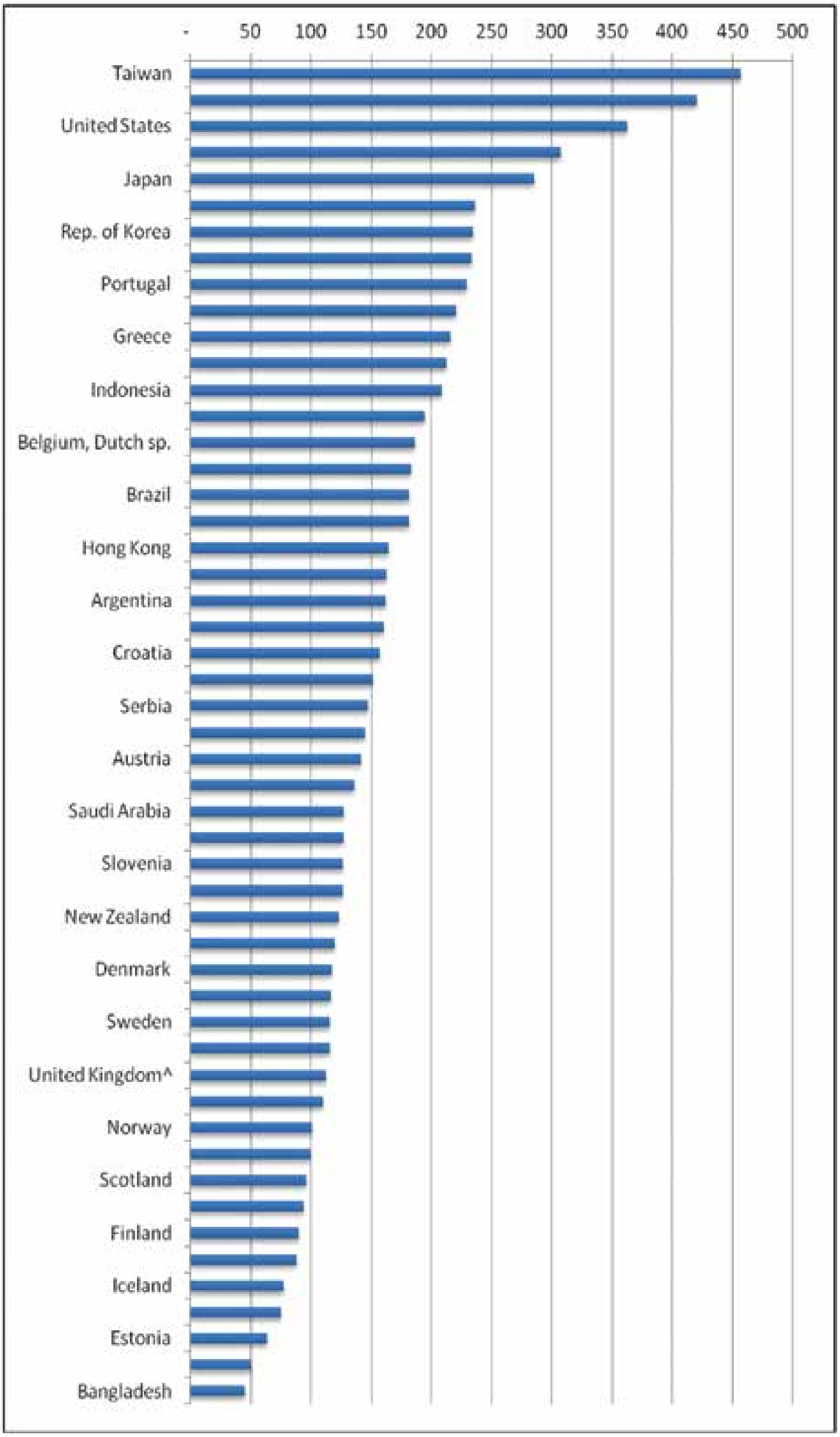
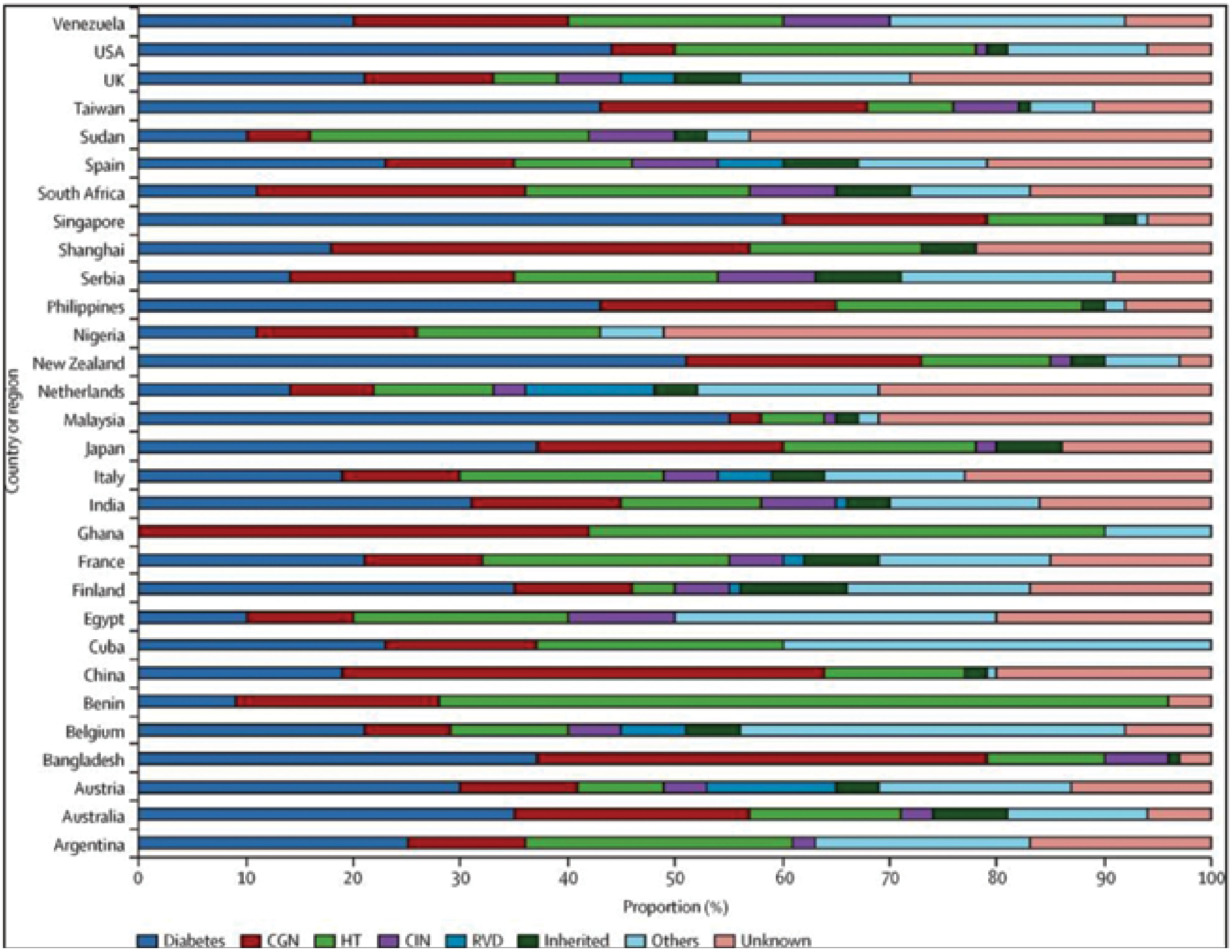


Figure 3. International comparison of the distribution of causes of CKD where CGN=chronic glomerulonephritis; HT=hypertensive nephrosclerosis; CIN=chronic interstitial nephritis; and RVD=renovascular disease. (taken from Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. Lancet. 2013 Jul 20;382(9888):260-72. doi: 10.1016/S0140-6736(13)60687-X. Epub 2013 May 31)



in Andhra Pradesh have for several years witnessed a massive increase of CKDu, with over 4000 deaths. Media have repeatedly reported the existence of the problem, and investigations are ongoing. One of the investigation has focused on drinking water as a source of the CKDu excess but inorganic contaminants appears unlikely.(6) Also, there are other rural areas in India, where NGOs and local kidney foundations report an increase of CKD, especially in agricultural workers. It has however been difficult to find comprehensive information in scientific or governmental reports.

Published scientific papers. Overall, most original articles and review papers report an increase of CKD related to aging populations, and an increase of hypertension, diabetes and metabolic risk factors. Smoking as a risk factor is also often assessed, as is use of potentially nephrotoxic pharmaceuticals and herbs. There is little or no information on occupational and environmental factors, and seldom descriptions of the natural and socioeconomic circumstances in the populations studied, neither on an individual nor on an area level. A limited literature search, with focus on identified countries of interest was performed. This literature search is by no way complete, but may serve as an illustration of the scarcity of information relevant for CKDu.

Pakistan: From Pakistan, identified as a hotspot, a series of papers describe results from a national comprehensive household health survey in 1990-1994, with more than 18 000 participants. Interestingly, a more than six-fold increased risk of dip-stick proteinuria (adjusted for age, diabetes, hypertension, BMI, smoking and some other potential confounders) was observed in the ethnic group of Sindhis.(7) This is also the population living in the lowland, with agriculture as the dominant economy and in the hottest parts of the country. Notably, hypertension was more prevalent in other ethnic groups.(8)

A marked difference in CKD prevalence between SEEK screening centers participating in a nation-wide study in India 2005-2006 was observed, with the highest prevalence (40%) among adults in Andhra Pradesh, where CKD had been reported as an endemic disease.(9) In reports from the Indian CKD registry, it was noted that underprivileged patients at governmental hospitals were younger and more likely to present at late CKD stage, with undetermined etiology.(10).

The use of traditional herbs, with aristolochic acid as a known nephrotoxin, is reported in several studies from Taiwan (11-14) and China (12-14). Another contaminant, ochratoxin, is also considered to be a risk factor for CKD in North Africa (15).

The potential effect of arsenic exposure on renal function has been explored in studies from Bangladesh, Taiwan and Chile. There may be slight effects on eGFR, but seemingly not of a magnitude that is comparable with clinical CKD disease. (16)

From Australia, an increased prevalence of CKD in the aboriginal population is well described, attributed not only to socioeconomic and life-style factors, but also to prenatal adverse effects, resulting in a lower number of nephrons, and thus an increased susceptibility for future insults. (17)

The importance of good childhood kidney health, ranging from optimal fetal development to absence of childhood urogenital infections, which has profound implications especially in deprived populations, has also been clearly advocated. (18)

What do we need to know?

- The spatial distribution of CKD and CKDu, at regional and sub-regional scale, including changes over time
- CKD prevalence in different age strata, including changes over time
- CKD prevalence in different population strata, including changes over time
- CKD prevalence in different occupational groups, including changes over time
- The distribution of known and suspected risk factors in the general (non-diseased) population
- The distribution of known and suspected risk factors in diseased populations

How can we move forward?

- More effective use of already existing data

In countries where mortality registries and population registries provide data on regional and district level, modern geographical information system (GIS) tools can be used to combine health and socioeconomic information with data on temperature, elevation, land use, and other spatially distributed data. Figure 4 provides an example of this applied in Costa Rica. Such additional data can be retrieved from existing national data sources as well as from satellite data. In this way temporal and spatial variations in CKD mortality within a country can be visualized.

Such spatially distributed information may shed light not only on environmental but also on occupational exposures, but only when such exposures are geographically distinctly localized, e.g. different types of agriculture, or mining activities. For other occupations, e.g. construction work, this approach is not feasible.

Figure 4. Mortality Rate Growth from 1980 to 2012 (Slope of change of the Mortality Rate)

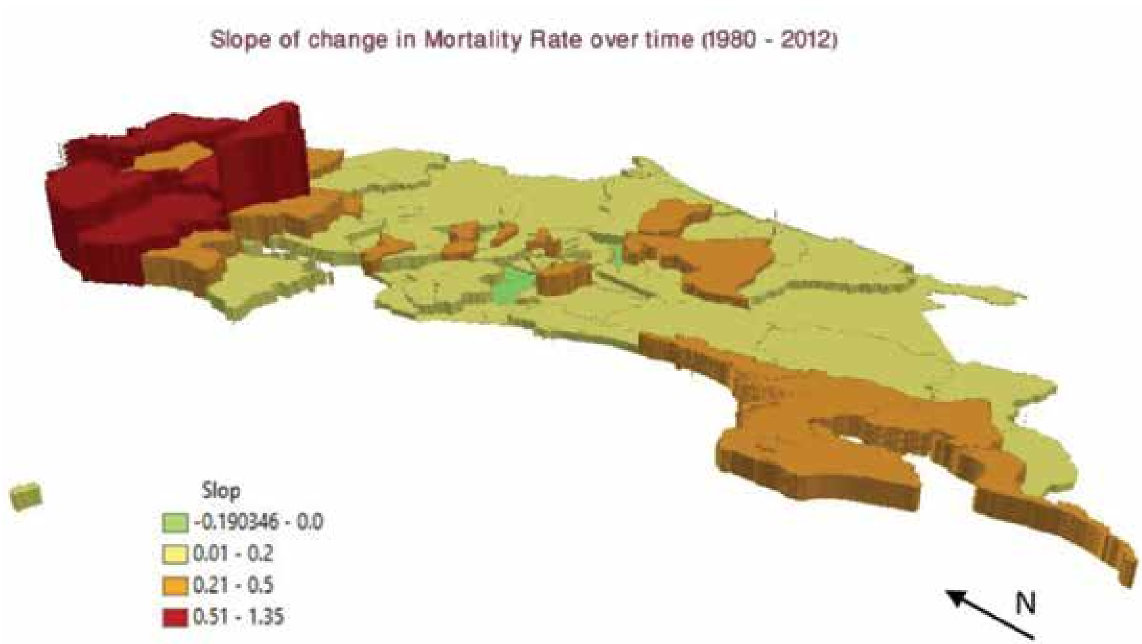
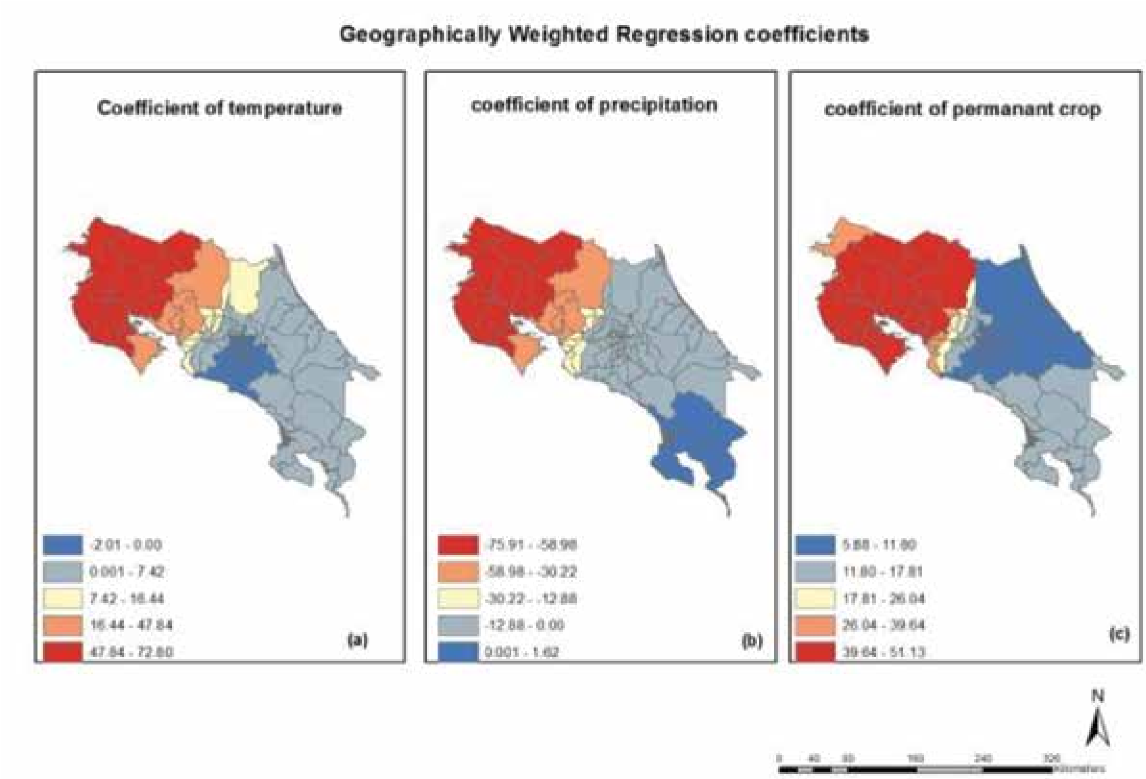


Figure 5. GWR coefficients for all independent variables



A GIS analysis from Costa Rica – spatial co-location of the highest mortality rate increase 1980-2012 with highest temperature, lowest precipitation and land area with most permanent crops. By courtesy from Ali Mansourian, GIS center, Lund university, Sweden.

- Re-examination of existing prevalence studies. Usually the existing publications have focused on identification of the traditional risk factors – diabetes, hypertension and smoking, with no or very limited information on occupational and environmental conditions. For some of these prevalence studies, it might be possible to go back and use existing knowledge of the screened population and their living conditions (soft data, data on area level, or not yet analyzed or reported individual data) to describe the "unknown" risk factors for CKD.

- New prevalence studies using a protocol based on screening both for eGFR and proteinuria, with information on former and present occupational activities, and with good descriptions of the environment in the study area. From prevalence studies on kidney function in developed as well as developed countries, it is well known that the majority of cases with decreased kidney function were not previously known. Unfortunately, low-budget prevalence studies in developing countries often have been conditioned on dipstick screening as a first step, followed by determination of S-Cr only in cases with proteinuria. Such a strategy will miss early and sometimes even advanced CKDu cases with a clinical picture similar to the disease entity observed in Central America as well as in Sri Lanka.

▪ Feasible study designs to investigate renal health in migrant workers (an intriguing example is Nepalese construction workers returning from the Gulf states, anecdotally reported to have an increased risk of CKD after return)

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In which countries and occupations has CKDu been reported in excess and how well has it been studied where there are no reports? South and Central America

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What do we know?

Prevalence studies that present data on Chronic Kidney Diseases of unknown etiology (CKDu) are rare, and registries of patients in replacement therapy are voluntary, frequently omitting the number or percentage of patients with CKDu. Very few countries have any information on the prevalence and distribution of CKDu within the country. Some countries have means to estimate the incidence and prevalence of the population with end-stage renal disease (ESRD) that are in replacement therapy, when access to health care services is high, and data on morbidity from different sources are available for analysis, as in Brazil, for example. We will present some information collected from peer-reviewed papers, a preliminary analysis of within country variation of CKD incidence and prevalence in Brazil, and estimates of CKDu in some countries based on voluntary registries.

Mortality data remain the most reliable information available from all countries. The PAHO mortality registry database is available online, with easy-to use modules for data retrieval and pre-set data visualization.(1) However, it is important to note that there remain some problems with the mortality data that should be taken in consideration in any analysis.(2) One limitation is the delay in reporting, most Central American countries are included through 2013 but El Salvador is only included through 2012.(2) Other limitations are coverage and data quality. El Salvador and Paraguay report 19% and 10% respectively of "ill-defined and unknown causes of death".(2) Mortality under-registration can go up to 39% (Peru), being approximately 21% in El Salvador and 25% in Nicaragua.(2) There are large differences in death certificates with respect to how ICD10 is used, among other problems. It is not possible to separate CKDu using the mortality data available, but it is possible to explore differences on CKD mortality among countries in the Region, which will be presented.

Population based prevalence and incidence studies

A systematic search of published literature reveals few studies on national population prevalence or incidence of CKD in Central, South America and the Caribbean.

One report explored prevalence and regional variation of CKD among an older population in **Costa Rica.** This study used data from the Costa Rican Longevity and Health Aging Study (CRELES) and relied on defining a case of CKD based on a measured eGFR<60 ml/min/1.73 m^2.(3) An estimated 20% of older persons (60 or older) met the case definition. CKD occurred slightly more frequently among women (21%) than men (17%). CKD prevalence among elderly (adjusted for traditional CKD risk factors) was higher at higher altitudes but also demonstrated a striking regional variation with two lowland provinces, Guanacaste and Limón, the former a known endemic CKDu region in Costa Rica, standing out for their high prevalence.

In **Peru**, a population-based study (CRONICAS) found an overall prevalence of CKD (eGFR<60 ml/min/1.73 m^2) of 16.8%. Similar to the population study from Costa Rica, but unlike regional studies from Central America, prevalence in women was higher (23.4%) than in men (10.3%). The authors also note that older age and being diabetic were independent predictors of CKD. There is no mention of CKDu (4).

Some estimates of population-based incidence are available from **Colombia,** where 52% of the population is estimated to be covered by the social security system. Using 2004 data from that system, it is estimated that the most important causes of incident chronic renal failure are diabetes mellitus (33%), hypertension (29%), glomerulonephritis (8%), and other causes including unknown causes (30%). The average age of the incident patients was 54 years. (5)

One report of CKD in a specific ethnic group comes from **Argentina**. The adjusted (age and gender) prevalence of CKD in Toba aborigines from the Chaco province was estimated at 5.5% (CKD Stage 3); 9.5% of them had diabetes, and 76.2% arterial hypertension.(6) The authors do not present the percentage that is unrelated to both risk factors. Proteinuria was highly prevalent in the age group >45 years, though unrelated to deterioration of eGFR, which the authors report as similar to findings from Australian aborigines.

A report of prevalence of CKD for specific subpopulations within country is provided in the paper by Trujillo and Correa-Rotter in this report. (7)

Morbidity based on registry of treatment of ESRD and RRT

In most Latin American countries reporting is voluntary and few countries have information concerning chronic kidney disease of unknown etiology **(Table 1)**. The quality of the data from the regional registry is determined by that provided by the national registries. The heteroge-

Table 1. Prevalence and incidence of RRT in Latin America in year 2010.(8)

Country	Prevalence (per 10^6)	Incidence (per 10^6)	% CKDu
Nicaragua	37	ND	-
Guatemala	123.3	10.7	-
Paraguay	148.7	33.3	-
Bolivia	153.1	ND	-
Dominican Republic	165	ND	-
Honduras	187.2	197.1	-
Cuba	303.9	99	-
Peru	335.3	34.3	-
Costa Rica	338.8	ND	-
Ecuador	405.9	127.7	-
Venezuela	457.4	ND	-
Panama	517.3	ND	-
Colombia	533.1	141.9	-
El Salvador	562.4	ND	-
Brazil	708.7	173.7	8-42% (9,10)
Argentina	777.8	152.5	25% incident; (≥40% are >50 yo) (11)
Uruguay	1,031.10	161	-
Chile	1,136.70	174.9	22% in dialysis (12)

neity or even absence of registries in some Latin American countries is congruent with the inequities for ESRD patients in access to RRT in such countries, as well as the availability of qualified personnel.(8)

A study case: Brazil

Sesso et al surveyed RRT centers in 2013 on behalf of the Brazilian Society of Nephrology.(9) Half of the 658 units registered by the Society and actively treating chronic CKD patients completed a survey of prevalent cases. The prevalence of RRT was reported as 499 patients per million inhabitants, with large differences between the regions of the country: North (284); Northeast (358); Center-West (589); South-East (597); and South (622). Patients were more commonly male (58%) and almost two-thirds (62.6%) were between 19 and 64 years of age.

Using a different data source, Moura et al evaluated all patients (2000-2012) with ESRD defined as those with reimbursement from publically financed dialysis for a minimum of three months to eliminate cases of acute renal failure. A total of 280,667 patients were identified, estimated to account for 85% of all patients in RRT in Brazil. The distribution of patients based on race was similar to the general population according to the Brazilian census. Prevalence of ESRD increased 47% in the period; incidence increased 20% in both sexes and in all regions of the country, particularly in older age groups (10).

Assessment of unknown causes of CKD proved difficult when these two data sources were compared. Based on a self-assessment survey, Sesso et al reported that only 8% of the cases were from ill defined or unknown etiology (9). By contrast Moura et al, using a much larger data set recovered directly from the notifications of the SUS (Brazilian Unified Health System) payment system, reported 42.3% of cases as undetermined.(10). A study in São Paulo reports high rates of CKDu in patients in RRT who have never visited a nephrologist prior to RRT (24). It is evident that, without complete and systematic assessment of causes of CKD, the proportion of patients without known causes will not be consistently reported.

An exploratory study in Brazil

Based on the same SUS database used by Moura et al (10), we have done an exploratory analysis of the within country distribution of the 42.3% of the cases identified as CKDu for the period between 2009-2012, which is presented here (unpublished data). Details of the methods used for the linkage of the databases and for the current estimates have been published by Moura et al (13). In the CKDu group, approximately 60% of the study population was male, a proportion that did not vary by regions of the country. The distribution of the overall

Table 2. CKDu adjusted rates*, all ages, 2009-2012, Brazil

Region	States	2009	2010	2011	2012
Center-West	MT, MS, GO, DF	48	48	53	56
North-East	MA, PI, CE, RN, PB, PE, AL, SE, BA	46	46	50	55
North	AC, RO, AM, RR, PA, AM, TO	36	41	31	30
South-East	MG, ES, RJ, SP	72	73	76	74
South	PR, SC, RS	74	76	90	87

(*rates /106 adjusted for the Brazilian population)

Figure 1. CKDnT incidence rates*, Federal Unities (States), Brazil, 2012 (* rates /106, unadjusted)

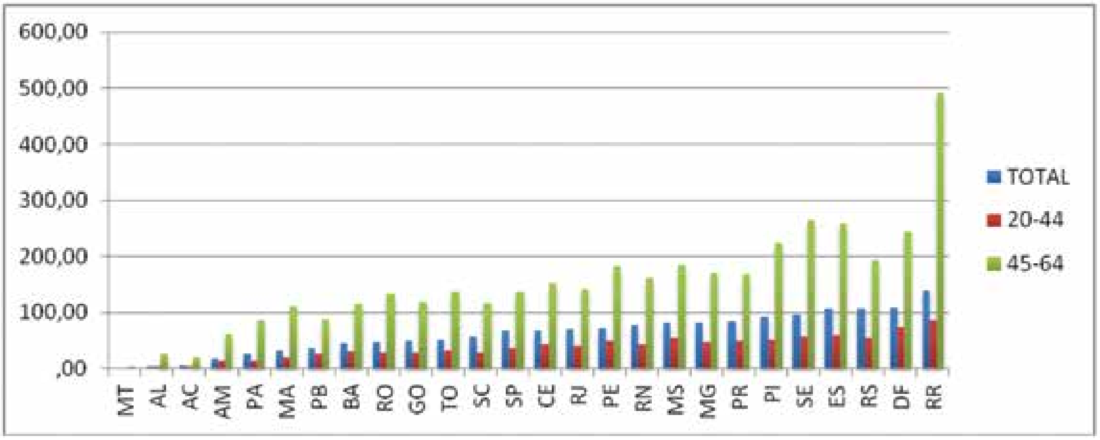

Table 3. CKD premature mortality (N17-N18) rates* male and female, Americas, 2001 and 2010 (Source: PAHO mortality database)

Country	2001		2010		Rate Difference
	Rate	male/female	Rate	male/female	
Argentina	10.62	1.7	9.87	1.6	-0.8
Bolivia	9	1.1	na	NA	-
Brazil	6.33	1.6	5.93	1.6	-0.4
Chile	5.78	1.6	5.98	1.5	0.2
Colombia	5.8	1.5	6.29	1.4	**0.5**
Costa Rica	6.13	1.8	7.66	2.1	**1.5**
Cuba	3.28	1.1	3.41	1.2	0.1
Dominican Republic	4.38	1.6	3.68	2.0	-0.7
Ecuador	15.28	1.2	10.36	1.5	-4.9
El Salvador	47.2	3.1	66.6	3.3	**19.4**
Guatemala	na	NA	24.74	1.2	-
Honduras	na	NA	2.75	1.5	-
Mexico	12.36	1.2	10.66	1.5	-1.7
Nicaragua	24.15	3.6	44.7	4.4	**20.6**
Panama	8.26	1.9	10.86	2.7	**2.6**

Country	2001		2010		Rate Difference
	Rate	male/female	Rate	male/female	
Paraguay	8.59	1	12.08	1.4	**3.5**
Peru	10.4	1	11.32	1.1	0.9
Uruguay	3.71	1.4	4.69	1.3	**1.0**
Venezuela	na	NA	8.43	1.4	-
Total	7.42	1.4	7.35	1.5	-0.1

* age-adjusted mortality rates

CKDu rates per regions of the country adjusted for the Brazilian population is presented in Table 2, and shows higher rates in the South-East and South regions. However, the states presenting higher rates of CKDu are not only concentrated in these regions. Figure 1 shows the unadjusted rates per million of the population by the Units of the Federation (states) for the year 2012, comparing the total rates, and those for the age groups 20-44 and 45-64 years of age. This figure clearly shows higher rates in the group 45-64 years. There are large differences in the population size, age distribution, and specialized RRT services in different areas of the country, which may explain, at least in part the differences observed. More in depth analysis is needed to understand this distribution.

Mortality database

In the Americas as a region, the age-adjusted rate from diseases of the urinary system is the 10th cause of death, and in the age group 30-69, it is the 13th. In El Salvador during 2012, disease of the urinary system was the first cause of mortality regardless of age, with highest rates among those in the age group 30-69 years. In Nicaragua, it was the third and second respectively in the same group ages, In the same year, in Peru, it was the 5th cause of death in all ages, but the 8th in the group 30-69 years. It was also amongst the first 10 causes of death in the following countries (rates not adjusted): Argentina (6th), Brazil (10th), Colombia (9th), Costa Rica (9th), Ecuador (9th), Guatemala (8th), Mexico (8th), Panama (6th), Paraguay (9th), United States (9th), and Uruguay (8th). However, only in some of these countries this group of diseases remains within the first causes of deaths in the age group 30-69 years, the group of interest for prevention of non-communicable diseases. CKD mortality rates (N18) is > 10/100,000 in Nicaragua (42.8), El Salvador (41.9), Guatemala (13.6) and Panama (12.3).

Table 3 shows adjusted CKD premature mortality rates for 2001 and 2010 (best available data for comparison between countries) along with the male/female rate ratios. For some countries, the male/female ratio is more than 2.0 in both periods.

CKDnT and occupation

Although MeN is often described as an epidemic of agricultural workers, in Central America sugarcane workers are clearly the most affected population (14). Several studies suggest that MeN may also occur among miners and construction workers (15,16), cotton workers (17), and subsistence farmers.(18) However, these are all cross-sectional studies and most collected data are on current occupation and are therefore not conclusive. In addition, cane cutting is seasonal and many sugarcane workers are also subsistence farmers or work in construction. Two studies did not find an increased risk among subsistence farmers (16, 17). Contrary to contract workers, independent small-scale farmers have control over their work hours and are able to avoid the hottest temperatures. Furthermore they are autonomous on the decision about the use of agrochemicals.

This group should be better studied to inform targeted policy actions.

In Brazil, from the 1980s to 2006, the amount a sugarcane harvester cuts has increased from four tons to 12 tons a day (19). Payment is received by amount harvested, and the increased demand of this work was appointed as the cause of death of 21 manual sugarcane harvesters at work in the interior of São Paulo between 2004 and 2007. Among them were young migrant workers from other regions of the country, especially from the Northeast (20,21). There are estimates from a study performed in the beginning and in the end of a harvest season with 28 healthy sugarcane workers in São Paulo, Brazil. At the end of the daily shift of the season, all individuals presented a decrease of the estimated glomerular filtration rate by approximately 20%. 18.5% presented serum creatinine increases. The changes were associated with increase of CPK and other biomarkers of renal damage, systemic inflammation, dehydration, oxidative stress and rhabdomyolisis (22).

Migrant workers

In Costa Rica there seasonal workers frequently come from Nicaragua for the sugarcane harvest activities (23). There are a number of other studies showing that internal migrant workers are an important part of the workforce in sugarcane plantations in São Paulo (20). It is necessary to understand and take into consideration the migration flow of the workforce to between countries or regions within a country during the harvest season, when searching for possible areas with high concentration of cases of CKDnT.

What do we need to know?

More attention should be given to the reasons for high rates of CKD of unknown etiology in some of the countries in the Region.

Prevalence studies have been recommended to assess exposure to CKD risk factors and kidney dysfunction in different occupations.

There is an urgent need to review the evidence and quantify the health risks that payment-for-production represent for the workforce.

The impact of the migration flow of the workforce during the harvest season on the prevalence of CKDnT within and between countries.

How can we move forward?

Focus future studies in places most likely to present the same type of working conditions as in Central America, and explore patterns of the distribution of CKD within regions of the countries to identify potential areas and occupations where the prevalence rates are higher in younger ages. We need more information on migrant workforce.

As pointed by recent analysis from PAHO, health statistics bureaus in countries in the Region of the Americas are implementing information systems to produce reliable, timely, valid and accurate data. Several countries have improved their systems in the last years, mainly regarding mortality. However, challenges remain regarding morbidity and epidemiological surveillance. Health information systems need to be strengthened in the region, including provisions for a national registry of patients in dialysis.

We need an agreed list of “suspected causes” that would support the improvement of the ICD 10 codes for CKD, including “associated causes” that could also be used in death certificates. This would help standardize information, and would facilitate the identification of CKDnT.

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Epidemic of CINAC in Sri Lanka (CKD in Sri Lanka)

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Introduction

During the last two decades, a significant increase in the Chronic Kidney disease (CKD) cases has been observed in the dry zone of Sri Lanka, especially in the North Central Province (NCP). Two main climatic zones are recognized in Sri Lanka: the wet zone that occupies the South, West and Central regions, and the dry zone, which occupies North, North Central and Eastern regions of the country (Figure 1). In the dry zone average annual rainfall is 1000–1500 mm that mainly occurs during the Northeastern monsoon period [1]. NCP is a major rice cultivation area where two districts, Anuradhapura and Polonnaruwa, contribute 19–23% of the total rice production of the country. This unusual CKD was first reported in 1994 among middle-aged paddy farmers in Padaviya region in the NCP [2]. In this epidemic the etiology of the CKD was unknown. Therefore, initially the term CKD of unknown origin (CKDu) to identify these patients was used. However, and considering the epidemiological and histopathological findings, the disease is now named as Chronic Interstitial Nephritis in Agricultural Communities (CINAC).

Twenty years after the first report, CINAC is the most significant public health issue in the NCP with more than 69,000 estimated patients and many deaths [3]. The disease is spreading in epidemic scale to other adjacent farming areas in the Eastern, North Western and Uva provinces of Sri Lanka. The affected area covers one third of Sri Lanka's landmass. Interestingly only very few patients were reported from Northern province of Sri Lanka which shares similar soil, climate, agriculture and occupational patterns with CINAC endemic regions (Figure 2).

Prevalence

The underlying cause of renal failure was not identified in 82% of CKD patients seen at the renal clinic at Anuradhapura teaching hospital between 2000 and 2002 [4]. The WHO study group reported age-standardized prevalence of CINAC higher in women 16.9% (95% CI = 15.5%–18.3%) than in men 12.9% (95% CI = 11.5%– 14.4%), but noted that more advanced stages of CINAC were seen more frequently in men (stage 3, men 23.2% and women 7.4%; stage 4 men 22% and women 7.3%; $p < 0.001$) [5].

Clinical profile

The CINAC is a disease that progresses slowly. Patients are asymptomatic during the early stages of the disease. Athuraliya and others reported the symptom profile of CKDu patients (n=109) was essentially normal, except for the raised serum creatinine (2.51±2.06 mg/dl) and small bilateral echogenic kidneys (mean relative bipolar length 5.36±0.91 cm). Urine samples had no active deposits, few having hyaline or granular casts [6]. The disease is characterized by tubular proteinuria (alpha-1 and beta-2 microglobulin) and high urine N*eutrophil Gelatinase-associated Lipocalin* (NGaL) levels (>300 ng/mg creatinine/dL) [7]. Nanayakkara and others showed urinary excretion of alpha-1 microglobulin was elevated in CINAC patients at early stage indicating that renal tubular damage and tubular epithelial dysfunction occurs early in CINAC [8]. Slow progression, minimum urine proteinuria without active sediment, bilateral small echogenic kidneys and long-standing hypertension in the absence of diabetes strongly favor a tubulointerstitial disease. Another study shows significant elevation of serum uric acid levels (7.83±1.32 mg/dL) in CINAC patients when compared to healthy individuals (5.14±2.87 mg/dL) [9].

Diagnosis

In 2009, the Ministry of Health (MoH) of Sri Lanka introduced three criteria to differentiate CINAC from usual CKD [10]:

a. No past history of, or current treatment for,

diabetes mellitus or chronic and/or severe hypertension, history of snakebite, urological disease of known etiology or glomerulonephritis.
b. Normal Glycosylated Hemoglobin level (HbA1C<6.5%).
c. Blood Pressure <160/100 mmHg untreated or < 140/90 mmHg on up to two antihypertensive agents.

Wanigasuriya and others have used different criteria for their published research. They recruited patients with a serum creatinine greater than 2 mg/dl with no obvious underlying cause [11]. Athuraliya and others have used proteinuria detected on two out of three time points, (during a period of 3-4 months in early-morning clean-catch spot urine sample) by dipstick and confirmed by heat testing as a screening tool [6]. The WHO study group used albumin–creatinine ratio ≥30 mg/g creatinine in an initial urine sample, confirmed at a repeat visit, to identify CKD patients. They also used MoH's criteria to distinguish patients with CINAC.

Histopathology

Findings have shown tubular interstitial nephritis associated with mononuclear cell infiltration, glomerular sclerosis and tubular atrophy [12]. Athuraliya and others carried out 26 kidney biopsies and found renal fibrosis, glomerular sclerosis, tubular atrophy and active interstitial space with inflammatory infiltrate [6]. A retrospective analysis of 211 renal biopsies in asymptomatic CINAC patients revealed early disease among asymptomatic patients is characterized by interstitial fibrosis without significant interstitial inflammation, glomerular sclerosis and preserved glomerular function. Absence of hypertension associated vascular changes in the early stages of the disease makes hypertension an unlikely etiological agent. In late cases, hypertension is probably secondary to advanced renal damage [13]. In another retrospective study of 251 renal biopsies, Wijetunga and others have identified histopathological features of first four stages of CINAC in Sri Lanka [14]. The predominant feature of stage I disease was mild and moderate interstitial fibrosis while most cases did not demonstrate any evidence of interstitial inflammation. Stage II disease had moderate interstitial fibrosis with or without mild interstitial inflammation. Stage III disease had moderate and severe interstitial fibrosis, moderate interstitial inflammation, tubular atrophy and some glomerulosclerosis. Stage IV disease had severe interstitial fibrosis and inflammation, tubular atrophy and glomerulosclerosis. They show that initial renal injury is interstitial fibrosis without inflammation. According to them, a possible explanation is tubule epithelial injury due to chronic low dose exposure to environmental toxins. The other explanation is episodic exposure to high concentrations of toxins giving rise to acute tubulo-interstitial nephritis then healing by fibrosis showing progressive interstitial fibrosis. Furthermore, they have demonstrated the progression of the pathological features associated with failing GFR and argued that initial renal injury occurs at a young age. Tubulointerstitial disease with negative immunofluorescence for IgG, IgM and complement-3 are in more favor of excluding an infectious origin [6].

Etiology

Wanigasuriya and others described that being a farmer ($P < 0.001$), using pesticides ($P < 0.001$), drinking well water ($P < 0.001$) and in the field ($P < 0.036$), a family history of renal dysfunction ($P < 0.001$), taking ayurvedic treatment in the past ($P < 0.001$) and past history of snake bite ($P < 0.001$) were risk factors for CINAC [11]. Athuraliya and others found age more than 60 years (OR = 3.5, 95% CI = 1.6 to 7.4), being a farmer (OR = 2.1, 95% CI = 1.4 to 3.3), family history of CKD (OR = 2.9, 95% CI = 1.2 to 7.2) and exposure to agrochemicals (OR = 5.6, 95% CI = 2.3 to 13.2) were risk factors for CINAC. Further, they mentioned CKDu is unlikely to be due to analgesic use as the patients were not on long-term analgesics [6]. Bandara and others found elevated dietary cadmium (Cd) as a possible causative factor for the disease [15]. They reported high Cd content in lotus rhizomes, rice and tobacco, and concluded that the provisional tolerable weekly intake of Cd, based on extreme exposure through rice and fish, was high in the area. Meharg and others demonstrated the cadmium content in rice samples of Sri Lanka is high and only rice from Bangladesh had a higher content, when cadmium levels in rice grains from 12 countries in four continents were compared [16]. The WHO research group pointed out risk for CINAC was increased in individuals aged more than 39 years and those engaged in vegetable cultivation (OR = 1.926, 95% CI = 1.561 to 2.376 and OR = 1.195, 95% CI = 1.007 to 1.418 respectively, $P < 0.05$). Further, they showed pesticide residues were above the reference levels in 31.6% of those with CINAC. Detection frequency of 2,4-D, 3,5,6-trichloropyridinol, p-nitrophenol, 1-naphthol, 2-naphthol, glyphosate, and AMPA was 33%, 70%, 58%, 100%, 100%, 65% and 28% respectively [5]. They have also shown mean concentration of Cadmium in urine was significantly higher in those with CINAC (1.039 μg/g) compared with controls in the endemic and non- endemic areas (0.646 μg/g, $P < 0.001$ and 0.345 μg/g, $P < 0.05$) respectively. They found a significant dose-effect relationship ($P < 0.05$) between the urine Cd concentration and stage of the chronic renal failure as defined by National Kidney Foundation, USA. In the same study, authors reported urine concentrations of Selenium is low in CKDu patients [5].

Jayasumana and others have shown that the CINAC epidemic among farmers in the dry zone of Sri Lanka is associated with drinking well water, with history of drinking water from a well that was abandoned and with spraying glyphosate in paddy fields [17]. They also developed a comprehensive hypothesis to explain the occurrence of the disease. According to this hypothesis chemical nephrotoxicity due to herbicides, herbicide surfactants, heavy metals, high iconicity of the ground water and chronic repeated dehydration are the culprits of the epidemic [18,19]. Siriwardhana and others have shown in a study done in Medawachchiya, a CKDu endemic area in NCP, that working for more than six hours in the field per day under the sun ($P < 0.003$), drinking water only from well ($P < 0.006$), consumption of less than three liters of water per day ($P < 0.04$), and having a history of malaria ($P < 0.027$) are factors that lead to the development of CKDu [20]. However, the effect of heat stress and chronic repeated dehydration on CINAC has not been systematically studied in Sri Lanka. In a cohort study done by Senevirathna and others, it was pointed out that the proportion of early stage CINAC was greater in the younger patient group (66% of stage 1 patients are less than 30 years), while higher proportion of advanced CINAC (68.8% of stage 5 patients are more than 50 years) were seen in older groups [21]. In the same study, they have identified hypertension as the main factor for disease progression. A study done in Padaviya and Medawacchchiya showed that the majority of CINAC affected villages are located downstream, far away from the reservoirs and irrigation canals [22].

Certain compounds present in ground water and soil in the disease endemic area have been postulated as possible etiological factors for CINAC. Chandrajith and others hypothesized elevated levels of fluoride in ground water in certain areas in Sri Lanka could be associated with increasing prevalence of CINAC [23]. Jayawardana and others revealed that the number of CINAC patients is high in places where elevated concentrations of soil vanadium were observed [24]. Further, they recorded vanadium levels in nonagricultural soils of CKD-reported sites are significantly exceeding the maximum threshold level recommended for soil (200 mg/kg).

Dharma-wardana and others in 2014 presented a new hypothesis based on "increased ionicity of drinking water due to fertilizer runoff into the river system, redox processes in the soil and features of 'tank'- cascades and aquifers. The consequent chronic exposure to high ionicity in drinking water is proposed to debilitate the kidney via a Hofmeister-type (protein-denaturing) mechanism" [25].

Ocharatoxin A, a naturally occurring fungal toxin was also speculated as an etiological agent for CINAC in Sri Lanka. However, a study showed it is a natural contaminant of cereals and pulses cultivated in CINAC endemic area, and the levels detected were below the toxic limits [26]. Dissanayake and others identified cyanobacterial toxin as a potential nephrotoxin in the CINAC endemic areas [27]. Nevertheless, contamination of ground water in shallow wells and tube wells by cyanobacterial toxin has not been reported yet.

Nanayakkara and others identified genetic susceptibility as a risk factor for CINAC by using a genome-wide association study (GWAS) [28]. The GWAS yielded a genome-wide significant association with CINAC for a single nucleotide polymorphism (SNP; rs6066043; $p=5.23\times10$ in quantitative trait locus analysis; $p=3.73\times10$ in dichotomous analysis) in *SLC13A3* (sodium-dependent dicarboxylate transporter member 3). For this SNP, population attributable fraction was 50% and odds ratio was 2.13.

The differences in the incidence of CKD among patients exposed to similar environmental conditions and risk factors suggest that a singular risk factor is unlikely to be responsible for CINAC. It is more likely that an interaction between the proposed risk factors could contribute to the eventual development of the disease.

Prevention

CINAC is a multifarious issue requiring multipronged, short, medium and long-term approaches. The search for solutions to CINAC must go beyond the bio-medical model. As CINAC is an irreversible disease, identifying and implementing all the known strategies to slow down the progression is mandatory. The author recommends the following measures to protect at risk populations:

- Social and political measures to guarantee nephrotoxin-free drinking water and ensure adequate hydration
- Minimize the usage of glyphosate base herbicides and phosphate fertilizers.
- Minimize the usage of sugar and sugary drinks by farmers.
- Promote cultivation and sale of traditional varieties of rice, vegetables and fruits, which are less dependent on agrochemicals.
- Develop a screening method based on early proximal tubular damage markers and extend community CINAC screening to detect early loss in renal function and to better characterize high-risk population and affected areas.
- Promote collaborative basic and clinical research in order to understand the pathogenesis of CINAC and identify protective strategies prevents its development and slows the progression.

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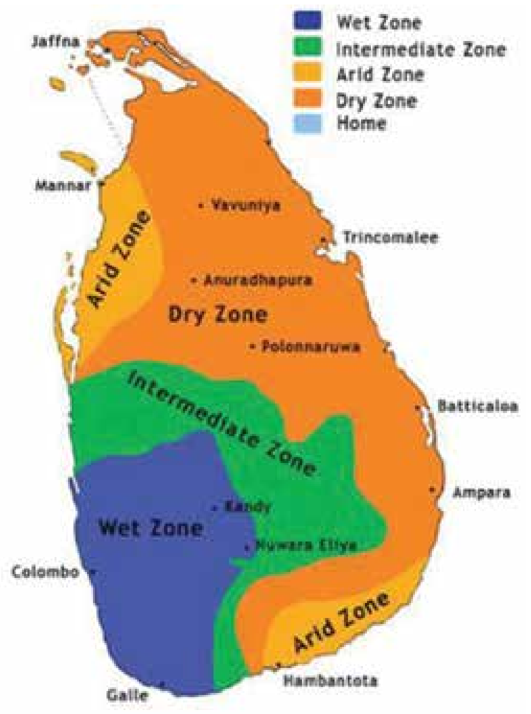


Figure 1. Climatic Zones of Sri Lanka

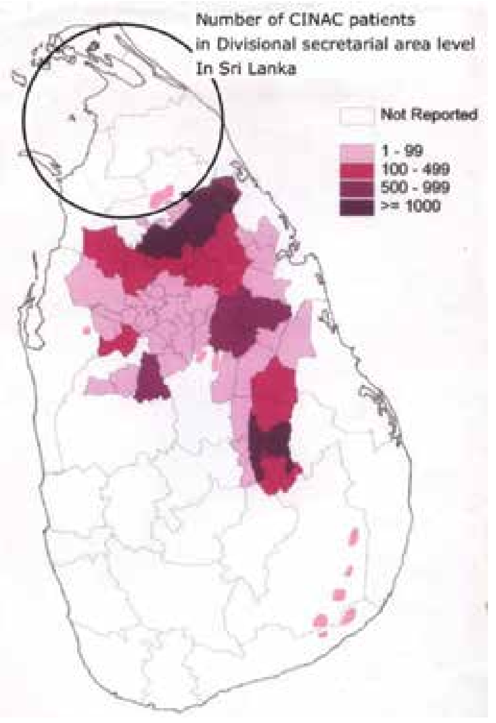


Figure 2. Geographical distribution of CINAC in Sri Lanka (Northern province is encircled)

Interventions, regulations and response of health care systems in Central America

Julietta Rodriguez Guzman, PAHO/WHO.

Introduction

The high incidence, prevalence and mortality rates of Chronic Kidney Disease from Non-traditional Causes (CKDu) in Central America, have increasingly been reported in underprivileged populations during the last two decades *(1)*, affecting agricultural communities where poverty and working opportunities are limited. The employment choices available in agricultural jobs occur in precarious working conditions and inequitable employment conditions. The majority of workers affected with CKDu are young men ages 18 to 35, farm workers, immigrants, and seasonal workers, concentrated in the Pacific coast of Mesoamerica *(2)*. Recent research has also shown early participation of children and adolescents in the workforce (*3*), as a consequence of the sugarcane monoculture, the endemic poverty in the region, and the need to alleviate financial pressures often resulting from death of a parent or family member caused by CKDu. These youth are even more susceptible to work under hazardous conditions, with low pay, and long hours, and uncertainty for their future (*4*). The high demand for tertiary level clinical healthcare services, - nephrology services offering dialysis, hemodialysis and kidney transplants -, has become a challenge for health care systems operating in the affected countries. This burden on health systems with limited resources has jeopardized the capacity to respond as well as the health and lives of the affected workers. Altogether, CKDu adds social and economic burdens to their families, communities, health systems, and society as a whole *(1,2)*.

Etiologic studies done during the last decade are not yet conclusive but strongly suggest known occupational causes, aggravating environmental factors, and social inequities, emphasizing the multi-causal etiology of the disease *(1).* While research teams continue to conduct studies about exposures to factors that seem to cause the kidney damage, countries have issued public health policies to address the problem, and health systems have led actions to detect and provide treatment when possible and to mitigate the consequences of CKDu. One intervention aiming to control hazardous and precarious working conditions has been piloted in an effort to document effectiveness and develop improved work practices for the long term *(5)*. This article addresses the interventions, regulations and responses of the healthcare sector at sub-regional, regional and country levels to mitigate and control the epidemics; address social gaps and propose some policy recommendations aiming to control the devastating human, social and economic effects of the epidemic.

Political willingness translated to policies and agreements addressing the epidemic

To better understand the breadth and the commitment of policy and decision makers at sub-regional, regional and national levels, a description of the actions carried out at these three levels follows.

a) Sub-regional level

The regional health sector of Central America and Dominican Republic has a long standing history of integrative efforts through the creation of several political and governmental bodies: The Central American Integration System (SICA[3]), the Council of Ministers of Health from Central America and the Dominican Republic (COMISCA[3]), and the Executive Secretariat for the COMISCA (SE-COMISCA[3]). During the past decades these bodies have designed and followed-up regional policies

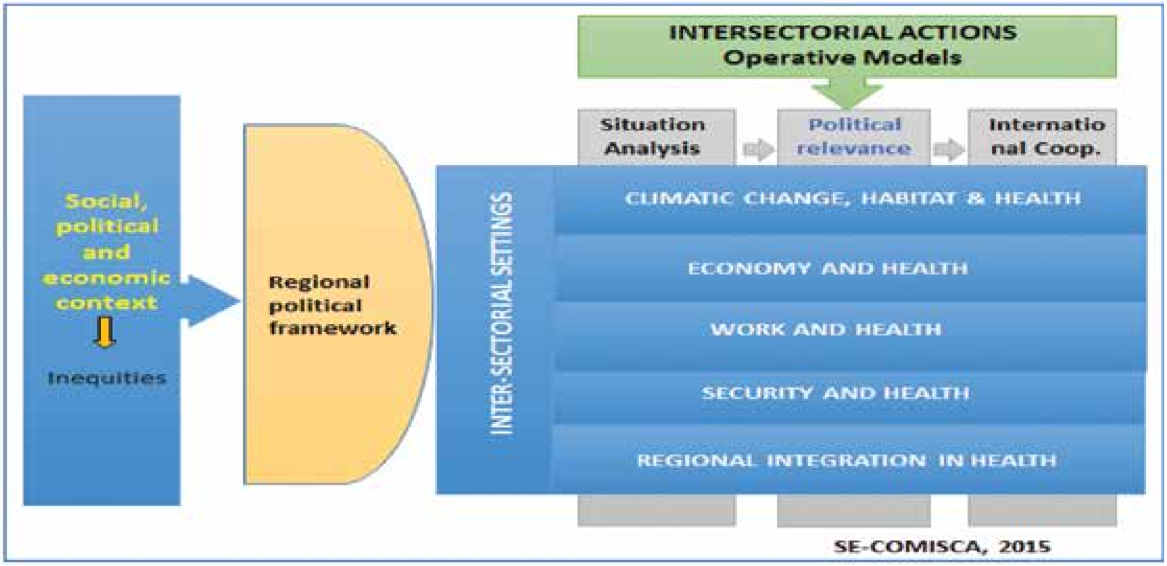
1. From its name in Spanish

Table 1. Sub-regional policy instruments of the health sector.

Year	Policy instrument
2009	Health Agenda for Central America and Dominican Republic; and, Health Plan for Central America and Dominican Republic (HPCA&DR), 2010-2015
2012	Preliminary mid-term report of the HPCA&DR, 2010-2015
2013	Amendments to the HPCA&DR, 2010-2015
2014	SICA Regional Health Policy 2015-2022 issued in 2014
2015	End-term report of the HPCA&DR, 2010-2015
2016	New Health Plan for Central America and Dominican Republic 2016-2020 was issued in December 2015 during the XLIII Meeting of the COMISCA

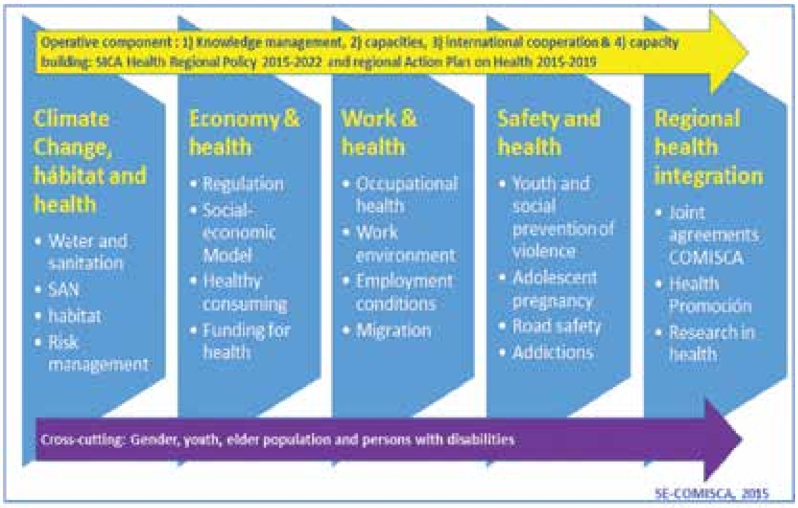
Source: Adapted from: Peña, R. Perspectiva de la CT con el SICA. Reunión inter-programática de OPS sobre Enfermedad renal crónica de las comunidades agrícolas de Centroamérica. Managua, Nicaragua, September, 2015.

Figure 1. Operative model of the regional political framework



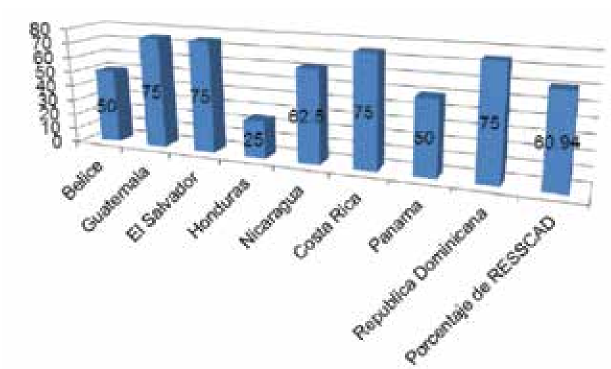
Source: Pena, R. Perspectiva de la CT con el SICA. Reunión inter-programática de OPS sobre Enfermedad renal crónica de las comunidades agrícolas de Centroamérica. Managua, Nicaragua, September, 2015.

Figure 2. Operative components and cross-cutting themes



Source: Pena, R. Perspectiva de la CT con el SICA. Reunión inter-programática de OPS sobre Enfermedad renal crónica de las comunidades agrícolas de Centroamérica.

Figure 3. Advances in the implementation of Agreement No. 2 of the XXX RESCAD 2014



Source: RESSCAD XXXI, Tegucigalpa, Honduras, October, 2015.

aimed to improve people's lives and wellbeing in the region. SICA advanced in building capacity, organizing technical and functional structures, and developing political agendas addressed to specific economic sectors. In the case of health, legal frameworks were developed to organize plans, strategies and agreements. Therefore, based on the Agenda of the Americas 2008-2017 *(6)*, they developed several policy instruments for strengthening regional and national public health policies *(7)*, as seen in Table 1.

However, policy instruments to assemble and coordinate all the regional efforts for effective public regional management were still needed. Thus, SICA issued the *Regional Health Policy 2015-2022,* that was approved during the Summit of Chiefs of States in December 2014. It serves as a political instrument that guides and allows active regional integration, through strengthening national actions and solving regional processes with an inter-sectorial approach. It also defines governmental actions to be developed at a regional level for complementing national competencies and responsibilities. It is based on a public health approach to achieving equity in health, addressing social determinants of health, and filling the gaps of the unfair and preventable health differences observed in the health situation of the countries belonging to the region, with the final purpose of improving people's health *(8)*. In the *Regional Health Policy 2015-2022*, health inequities are addressed based on the regional political framework, inter-sectorial actions in response to the situation analyses, political relevance of the topics, and opportunities for international technical cooperation. They aim to closing the gap of inequities in health, as shown in Figure 1. Each inter-sectorial setting depicts operative components that include actions on environmental and occupational health, addressing social and environmental determinants of health; and, cross-cutting topics that include human rights related to health, as shown in Figure 2. With this public health policy, SICA envisions supporting regional interventions and regulations for the time period 2015-2019.

The Meeting of the Health Sector of Central America and Dominican Republic (RESSCAD[1]) is a political forum of SICA that analyzes health problems, coordinates actions to build regional policies, and promotes the exchange and development of experience and knowledge about common health problems. RESSCAD supports and consolidates monitoring and assessment processes carried out for complying with the agreements done by Member States. However, it does not have enforcement capacity. It promotes strategic alliances and supports searching for technical and financial cooperation to address and solve health priorities under the integrated framework of SICA. It aims to using better the resources in each particular country and for the region, seeking for a better life quality for the population, and strengthening development for the health sector and the environment *(9).*

During the XXX RESSCAD held in 2014, countries recognized the complexity of the social determinants for CKDu, the need to close the gaps, strengthen healthcare systems, and to train healthcare personnel. In Agreement No. 2, countries committed to act with their health systems to carry out preventive and inter-sectorial actions upon traditional and non-traditional risks that could contribute to the origin and development of the disease. Emphasis was placed on the need to start individual and population interventions immediately to prevent CKDu even if etiology is not yet fully defined. Also, a sub-commission was created to address CKD led by the National institute of Health, of the Ministry of health of El Salvador, in close cooperation with PAHO, CDC and SE-COMISCA *(10).* This way, all agreements of COMISCA, RESSCAD and country efforts could lead to capacity building, and developing actions to minimize and control the CKDu epidemics, as a sub-regional health priority.

On October 2015, during the XXXI RESSCAD in Honduras, the balance of achievements on Agreement No. 2 showed that all countries were interested in starting a research agenda to characterize CKDu although the represented countries had advanced at different levels; that some countries had taken regulatory measures to control the disease; others had built capacity and developed clinical protocols for providing comprehensive healthcare services to workers and some regulations were issued too. Achievements between countries varied, with differences ranging between 25 to 75% of completed actions, and an average of 61% as illustrated in figure No. 3 *(11)*.

In December 2015, during the XLIII meeting of COMISCA, the Health Action Plan for Central America and Dominican Republic 2016-2020 was approved and launched. It contains a line of Action on Non-Communicable Diseases which will address CKD in general, but there is no specific mention of CKDu (12).

B) Regional level:

The Directive Council of the Pan American Health Organization (PAHO) recognized, in 2013, that CKDu affecting agricultural communities in Central America was a serious public health problem that required urgent, effective, and concerted multi-sectorial actions. This decision was made in response to a call for action from the Minister of Health of El Salvador, during PAHO's 52nd Directing Council *(1).* Consequently, PAHO organized an inter-programmatic working group that includes staff members from different departments involved in health services, health analysis, sustainable development and research at headquarters along with PAHO representatives of each of the Central American countries. The working group has focused on providing technical assistance and support to the countries, and coordinating activities with different stakeholders, namely delegates of the Ministries of Health of the countries (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama), professional medical societies (Latin American Society of Nephrology and Hypertension), SE-COMISCA, and PAHO collaborating centers on epidemiology, health analysis, and occupational and environmental health[4].

Activities carried out at the regional level during the last two years were reported during the 52nd Directive Council, September 2015*(2),* and can be summarized as follows:

a. Preparation of a set definitions for: clinical case of CKDu, epidemiological case and several mechanisms for improving epidemiological surveillance. The paper is still under discussion for reaching a consensus with all countries and all interested sub-regional parties, with support from CDC, the Latin American Society of Nephrology and Hypertension (SLANH), SE-COMISCA and delegates from member States;

b. Improvement of CKD mortality statistics with the help of PAHO's Latin American and Caribbean Network for Strengthening Information Systems for Health (RELACSIS, from its name in Spanish);

c. Countries and research groups incorporated CKDu in their research agendas, and carried out and published descriptive and analytical studies *(13, 14).*

d. Conducting a Delphi Survey to determine research priorities, aiming to define a Regional Research Agenda for CKDu. This activity is currently ongoing, despite the fact that many efforts have been done by the countries and research groups who have conducted studies and published many of their study results, including the Consortium for Nephropathy in Central America and Mexico (CENCAM) *(14)*.

e. Protocols for implementing preventive interventions on occupational and environmental health are currently on going in El Salvador with (NIOSH/CDC, IRET) the support of PAHO's Collaborating Centers on Occupational and Environmental Health, employing recommendations from the US Occupational Safety and Health Administration (OSHA) regarding strenuous work in hot climates. The first round of results seem promising although further validation of interventions such as *Water. Rest.Shade* and *Work Efficiency* will continue to be tested in 2016 (*5).*

f. PAHO set up and implemented an on-line course on diagnosis, treatment and prevention of acute pesticide poisonings *(15)*.

g. Advances in incorporating comprehensive care for CKD in health services, such as clinical guidelines at a primary level of care, updating national standards, and developing preventive and comprehensive care of CKD with emphasis on primary health care (PHC). El Salvador and Nicaragua established legal and regulatory frameworks for organ and tissue donation and transplantation.

h. PAHO reviewed essential drugs and technologies for CKD treatment with their possible inclusion in the list of qualifications for the PAHO Strategic Fund, although countries have not used it. PAHO also reviewed efforts to improve access and coverage of transplants as treatment for CKD.

> **1.** PAHO recently issued the Action *Plan on Workers Health 2015-2015 CD52/10 Rev.1*, in which countries committed to *strengthen diagnostic capacity, information systems, epidemiological surveillance, and research in the field of occupational diseases, injuries, and deaths.* They aim to *establish national research agendas to determine working and employment conditions and related inequalities; and generate practical solutions, knowledge, and evidence for decision and*

2. Regional Institute for study of Toxic substances (IRET from its name in Spanish), Costa Rica; the National Institute of Public health of Quebec (NIPH), Canada; and the US Centers of Disease Control and Prevention (CDC), and the National Institute on Occupational Safety and Health (NIOSH).

policy makers. In this sense, a specific indicator to tackle the epidemic was included for having *countries develop intervention or action protocols to minimize the occurrence of CKDu in Central America (16).*

i. Finally, a policy framework addressing the occupational nature of CKDu is under construction, also considering aggravating environmental and social factors that enhance the occurrence of CKDu. This is another reason why PAHO has prioritized actions to strengthen occupational and environmental health in the countries involved to minimize or mitigate hazardous exposures, and prevent the disease.

C) National policies and regulations issued by countries

The countries affected by CKDu have been addressing the problem with different levels of public policy definitions, national and international action plans. Some have undertaken policy actions based on existing regulations included in their Constitutional mandates, healthcare systems, social security systems, sanitary and labor codes, environmental health regulations, and occupational health and safety regulations. In particular, those pertaining to occupational health and safety such as labor codes, OSH guidelines, Lists of Occupational Diseases, etc., proved to be outdated and need to be brought up to date from the beginning of the first 2000 decade *(17, 18).* During the last 10 years some countries (Costa Rica, El Salvador) did update several regulations, and others have recently advanced in a similar way (Guatemala and Nicaragua). However, structural limitations dealing with human resources, capacity building and enforcement of regulations for workers' health remain to be achieved.

The Ministries of Health have taken actions to create awareness about CKDu, and triggered actions at national and international levels. The first country to raise the issue was El Salvador, who called upon the needs for public health intervention, and at the end of 2009, requested technical cooperation from PAHO to address the disease that had been widely documented in previous research and technical reports *(5)*. Later, the Minister of Health of El Salvador presented the CKDu problems to the COMISCA and SICA forums, and to the Pan American Sanitary Conference, at the meetings of the Group of the Americas during the 2011 World Health Assembly, and at preparatory meetings for the Region of the Americas prior to the United Nations General Assembly High-level Meeting on Non-communicable Diseases in 2011 *(19)*.

Member States belonging to SICA and COMISCA attended the *"High-level Meeting on Chronic Kidney Disease from Non-traditional Causes () in Central America"* in April 2013*(20)*. They discussed the gaps and challenges they had for addressing the clinical burdens of and the ways to prevent it, and issued the *"Declaration of San Salvador"* it which they recognized that the disease is a significant public health problem that required urgent action. They proposed a definition highlighting the fact that it mainly affected agricultural communities; described it as a catastrophic disease and a major health problem. As a consequence, the member states committed to organize and mobilize inter-sectorial resources needed at national and regional levels to control it *(21)*.

Following the agreements and policy mandates of the health ministers and the PAHO mandates aforementioned, countries have assembled task forces and designed national action plans, identifying their gaps and challenges to address the epidemics. While most countries focused on issuing regulations and strengthening health systems, statistics and clinical services to increase the responsiveness of clinical services for treatment of CKDu (dialysis), some countries issued regulations and organized national action plans to address and control probable hazardous exposures and working conditions causing kidney damage.

Based on the reports made by SALTRA and others gathered by PAHO's inter-programmatic working group for following-up and providing technical assistance to the countries affected by the epidemics, Table No. 2 summarizes the recent policy advances related to regulations, national plans, comprehensive healthcare systems, research and major challenges to be addressed *(18, 22, 23)*.

Table 2. Summary of advances in policy and regulations, national plans, health services and challenges of countries affected by CKDu.

Country	Regulations	National Plans	Healthcare services	Research	Challenges
Costa Rica	Decree for protection and rehydration of persons exposed to high temperaturewas issued.	National Council on Occupational Health discussing CKDu	Costa Rican Social Security Institution with MoH building capacities to register & follow-up CKDu cases (on-line reporting), and providing dialysis services, institutional and home services	Survey done by CCSS on CKD. SALTRA/IRET in the Secretariat of CENCAM.	Compliance of protective measures and insurance for workers. Having a national program on occupational health to address CKDu.
El Salvador	Regulations on OHS up-dated in 2004. Issued regulation forbidding 53 active ingredients of pesticides	• National Research Program for CKD/CKDu, Diabetes Mellitus, High Blood Pressure, CVD, Obesity and risk factors in the Salvadorian population	Integrated preventive and healthcare approach for CKD/CKDu. Strengthening PHC services. Increase # of nephrologists. Registry of Dialyses & transplants. Improve diagnostic technologies. Implementation of the Nefro Lempa project (3 levels of services) with PAHO, the Cuban National Institute of Nephrology and the Spanish AECID.	National studies trying to determine CKDu causes with national and international research groups. Registries of CKDu cases and mortality. Registry on dialysis.	National research agenda on genetics, congenital disease and cancer within people with CKDu. Intervention and cost research. Registries of CKDu cases Lab developments. Strengthening national policies on OHS and toxicology

Country	Regulations	National Plans	Healthcare services	Research	Challenges
Guatemala	Government approved Agreement No. 229-2014: National Regulation on Labor Health and Safety that includes issues for preventing CKD. Regulation under construction modifying management of domestic pesticides.	Action Plan for non-communicable disease (NCD) in Guatemala. National Strategic Plan on Occupational Health. Protocols for epidemiologic surveillance for CKD and CKDu were revised and updated.	Aiming to increase coverage, access and quality of healthcare services: ▪ Guidelines for addressing CKD & CKDu Lack of funding for medication, dialysis and transplants. Follow-up is being done through COMISCA and RESSCAD	Participated in several regional studies with the support of the Guatemalan Society of Nephrology, and SALTRA. Needs to establish national research agenda	Implementation and coordination with PAHO to advance in the pending agenda
Honduras	National Regulation: Renal Decree 200, 2013, to guarantee dialysis processes, improvement of healthcare facilities, and special support services for patients. Coming: Law for Social protection and National Health system	Template for registering CKD for revision of Nephrologists. National Plan for Water Safety. Decree to “Activate Honduras” for addressing NCDs. Research agenda on NCDs includes CKD.	MoH: establishment of a Unit for Data Management to register patients under hemodialysis in 2 cities. Services provided by the Honduran Institute of Social Security (>14,892 1st trimester 2015). U. of Kentucky: brigades for kidney transplants. Medications available.	Secretary of Health: has 15 research strategic lines, one for NCDs that includes CKD. Protocol to characterize CKD in Honduras is under construction.	Strengthening healthcare facilities, information systems, funding and new healthcare model. Defining CKD research agenda. Inter-sectorial approach to address risk factors and SDH.

Sources: Carmenate Milian, L, et al. SALTRA 2014 (17) PAHO (2014) Country reports on advances for implementation of PAHO Resolution CD52/8 (21). PAHO (2015) Country reports presented during PAHO’s Inter-programmatic meeting on CKDu, Managua, Nicaragua, September, 2015 (23).

Country	Regulations	National Plans	Healthcare services	Research	Challenges
Nicaragua	Law No. 456: "Additional risks and occupational diseases". Law No. 185, "Labor Code ", issued 15 June 2004, added Chronic kidney failure in Art. 111.	2013: Working group for elaborating the National Strategic Plan for Kidney Health in Nicaragua. Text under revision.	Law to donate and transplant organs, tissues and cells. Issued 9 October 2013. Limited installed capacities for hemodialysis. Medical education in nephrology is required. MoU with the Local health system of Chinandega to strengthen services.	National studies trying to determine causes of CKDu with national and international research groups. Hosted recent Latin American Congress of Nephrology where advances on the prevalence and characterization of the disease were brought by several research groups.	Patient associations in need of social and emotional support. Improving occupational & environmental policies and regulations. Cost analyses is needed to estimate investments adequately.
Panama	Executive decree No. 1510, issued on September 2014, established National Strategic Plan for NCDs. 2013: International meeting with COMISCA countries to develop a road map for CKD research. 2015: restrictions for application of pesticides.	National plan of NCDs included surveillance of pesticides as a risk factor for CKD. 2011: National Plan of kidney Health. Pilot project in Coclé, with early detection of CKD yield decreased waiting times, and increased capacity building. To be replicated in other parts of the country.	Participation in several workshops for surveillance on CKDu in 2013, and registration of dialyses and transplants in 2014. Moving towards expanding clinical healthcare service for early detection and treatment of CKD.	Panamanian Nephrology Association with PAHO, UNEP, INCAP, MoH and The Panama University developed a study about risk of pesticides, mycotoxins and metals for CKD. Diagnosis of CKD and risk factors in Coclé province, Panama, 2014.	Advancing in pesticide application and control Proposal for next RESSCAD: to control pesticide applications. Implement surveillance system for NCDs including CKD, dialysis and transplant registries. Expand kidney clinics. Strengthening OHS

Conclusions

1. Regional, sub-regional and national political levels recognize that CKDu is a major public health problem that needs multi-sectorial interventions to understand the dynamics of the disease, timely detection of workers at risk, and prevention and/or minimizing on-set of CKD.

2. Strong political willingness at all decision levels to address the epidemic is reflected in the advances shown in both the RESSCAD follow-up and the PAHO inter-programmatic follow-up. Nonetheless, information gaps about the magnitude and extension of the disease, as well as about efficacy of policy and actions undertaken still persist. Hence, efforts must continue at all decision levels in the affected countries to determine the magnitude of the population affected, implement effective preventive measures, and assess the impact of the clinical and preventive interventions carried out until now.

3. Regulations about health care systems, statistics and occupational and environmental health services seem to have significant differences between countries. This remains a challenge to be addressed by the countries at sub-regional level for providing reliable data that can be utilized by decision makers.

4. PAHO working inter-programmatic group agreed that despite the fact that etiologic studies are not yet conclusive, evidence gathered until now strongly suggest the occupational character of the disease, probably aggravated by environmental factors and social inequities, emphasizing the multi-causal etiology of the disease. Recognizing CKDu as an occupational disease and making it a compulsory epidemiological report, could help to understand the extent of the problem.

5. Many isolated and joint efforts have been done to address the CKDu epidemic and control it at the country level. However, most of the interventions done are focused on strengthening clinical services for curative purposes including very costly interventions such as transplants, rather than strengthening preventive occupational and environmental interventions which are less costly and could decrease the occurrence of the disease. This is a major challenge. Thus, strengthening occupational and environmental health policies, regulations and programs will contribute to preventing or mitigating the consequences of CKDu and to clarify its etiology.

6. All countries need to build capacity both for healthcare systems and occupational and environmental health teams, since actions carried out until now have not stopped the epidemics. Prevention should be enhanced at the workplace to avoid increase in the number of cases.

7. Evidence from research teams indicate a strong need to close other gaps such as those caused by the inequities of employment. Thus, actions to be taken by labor and agricultural authorities with a multi-sectorial approach. Research results supporting public workers' health and labor policies to improve these situations are strongly recommended.

8. Technical cooperation from regional and sub-regional bodies play a key role to advance the settlement of research agendas, preventive interventions and, lately, stop the epidemics.

The way forward

1. In response to the needs of the countries to address the CKDu epidemics, the PAHO working group moves towards having a complete inter-programmatic project that will provide technical assistance to build capacity for comprehensive health services that include:

- Workers' health promotion
- Preventive occupational and environmental interventions
- Curative and clinical interventions through strong healthcare systems at all levels of assistance (PHC, institutional and highly specialized services)
- Social support for affected families and sur vivors

2. A research agenda on CKDu that involves etiologic research and field research at the country level should soon be defined. PAHO is working strongly on this line, and currently conducts a survey to determine the agenda in the mid- and long-term.

3. Need to enhance policy-making for prevention, particularly in the field of workers' health, that should include:

a. Updating the official lists of occupational diseases in the countries aiming to have CKDu included in it.
b. Implementing occupational and environmental surveillance systems at the agricultural workplaces involved, or other sectors where the disease might appear.
c. Implementing field research and putting in place good work practices such as those proven to be effective and to improve workers' life quality and work performance (Water. Rest.Shade and the Work Efficiency WE).
d. Enforcing compliance with child labor regulations at the country level, and for the eradication the worst forms of child labor as conveyed in the II Global Meeting on Child Labor (Brasilia, 2013).

4. A policy statement regarding all PAHO recommendations is being drafted, and should include all the policy recommendations at the three decision-making levels.

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Heat stress and dehydration

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Background

At the 2012 workshop, heat stress and dehydration (HS/D) was believed by a majority of workshop attendees to be a key hypothesis based on the evidence available at that time, primarily:

HS/D is an exposure that occurs over a wide area, covering the areas of highest-reported incidence of CKDnT.

An occupational exposure that best fit the demographic characteristics of the disease, particularly its disproportionate occurrence among younger men, most notably in sugarcane workers. Of the variety of hypothesized occupational exposures, HS/D appeared the best fit for the range of industries identified as having high rates of elevated creatinine in cross-sectional seroprevalence studies pre-2012. These studies had found high rates of elevated creatinine not only in agriculture but, importantly, also in other industries requiring strenuous manual labor, yet without high exposure to agrichemicals (e.g., mining, construction, port work).

HS/D, particularly combined with strenuous exertion, is a well-known cardiovascular and kidney stressor, which can lead to acute kidney injury (AKI).

In 2012, evidence was preliminary and incomplete, and there was consensus that more knowledge was necessary to determine how important HS/D was as a causal component of CKDnT. The primary challenges facing the HS/D hypothesis following the 2012 workshop were:

The almost complete lack of epidemiological studies linking HS/D to CKD of any kind. Just one study from Thailand showed an association between self-reported occupational heat exposure and subsequent self-reported kidney disease diagnosis. In that study, neither the exposure nor kidney disease diagnosis was objectively determined.

The lack of evidence of CKDnT excess in many other areas of the world where HS/D conditions coupled with strenuous labor presumably exist. Specifically, evidence was lacking that a similar excess of CKD was occurring in other countries in which sugarcane was an important crop and largely harvested manually.

The lack of evidence for biologically plausible mechanisms for how HS/D causes CKDnT, particularly in the absence of acute kidney injury (AKI).

Since the 2012 workshop, advances in three main areas have provided new evidence regarding the HS/D hypothesis. First, potential mechanisms linking HS/D to CKDnT have been proposed, and supported by animal data. [1]. (See *"Proposed mechanisms for chronic kidney disease of uncertain etiology observed in Central America (Mesoamerican Nephropathy)"* in this report). Second, field studies that better document heat stress and health outcomes have been undertaken. Third, cohort and case-control studies (some including exposure and outcome data) that provide further information on the potential association between HS/D and CKDnT have been published. (Note: some of these studies have recently been summarized in a review by Elinder and colleagues [2]). Herein we summarize findings from the second and third areas.

Workload, heat stress and fluid balance in CKDnT-affected populations

Workload

Qualitative observational assessments of workload for sugarcane cutters have clearly shown that cutters carry out labor-intensive work [3-6]. To date in Central America, only a few job tasks in other industries, such as digging trenches or sack loading in warehouses have been shown to be of a similar intensity as sugarcane harvesting and sugarcane seeding [7, 8](Luis Blanco Romero, personal communication). Within a recent pilot study from the Worker Health and Efficiency (WE) Program in El Salvador, 45 workers wore heart rate monitors for one full workday. The majority of workers (28/45) spent over half the shift working at and above 50% of their predicted heart rate max [9]. Such heart rate intensities are higher than that maintained by soldiers during multi-day operations (30-40% aerobic power/heart rate max)[10]. Similarly, one study demonstrated that a group of Brazilian sugarcane workers (n=28) performed on average at 61% of their predicted heart rate max (estimated from an average daily work shift heart rate of 116 ± 11 beats per min)[11].

Heat stress

Sugarcane cutters work in hot and humid environmental conditions. Wet bulb globe temperature (WBGT, a composite measure of environmental parameters: air temperature, humidity, wind speed and radiation) has been measured during harvest periods in coastal sugarcane fields in Costa Rica, El Salvador and Nicaragua with highs reaching above 33°C WBGT in all cases and with average maximum air (dry) temperatures during the hottest parts of the harvest season between 34.0°C and 42.0°C [3-5]. In Brazil, similarly high dry bulb temperatures have been reported up to 35.0°C [11, 12]. Given the hot environmental conditions and strenuous workload performed by sugarcane cutters, OSHA guidelines stipulate that cutters should only work at 100% effort for 15-45 minutes per% hour in order to avoid the ill effects of heat exposure. In reality, workers rest infrequently in non-shaded area and therefore are exposed to excessive heat stress for a significant proportion of the workday. Indeed, the WE pilot study in El Salvador found that over the course of a harvest, cutters in the coastlands spent 40% of their time working in environmental conditions ≥30°C WBGT, when full effort should only be exerted for 25% per hour (calculated from hourly climate data collected over 102 workshifts) [13]. Further, in a study of sugar cane workers in Costa Rica, heat-related symptoms were reported more frequently by harvesters than by non-harvesters working in the same company [14].

Fluid balance

Several studies have attempted to measure changes in fluid status in workers. Urinary markers of hydration status (osmolality and density) remain the most commonly used, however, it was argued at the 2012 workshop that such urinary markers are relatively crude measures of acute changes in fluid status. Change in body mass has been difficult to measure and has given inconsistent results in the field [5, 15]. Urine specific gravity (USG) has been shown (even in workers drinking considerable liquid) to increase during the workshift in cane cutters [5, 11, 16].

Epidemiological studies investigating the association between HS/D and CKDnT

Pre-2012, epidemiological studies for CKDnT in Mesoamerica were limited to two community-based seroprevalence studies in Nicaragua [17, 18] and one similar study in El Salvador [19]. Since that time, a small number of epidemiological studies have been undertaken that have added to the working knowledge of CKDnT.

One case-control study was conducted in a greatly-affected community in northwestern Nicaragua [20]. Cases (n=78) were individuals with a measurement of eGFR<60 mL/min/1.73 m^2 obtained at a screening of community residents; controls (n=205) had eGFR>90 mL/min/1.73 m^2. Questions relevant to HS/D included an assessment among those with a history of agricultural employment (48 cases, 69 controls) of the time spent conducting a variety of work tasks over their working lives, and self-reported daily water and boli (rehydration packet consisting of water, sugar, flavoring, and electrolytes) intake during the workday. After adjustment for sex and age, any lifetime work as a cane cutter was strongly associated with reduced eGFR. Daily bolis at work was also associated with reduced eGFR, while amount of water consumption was unrelated. Limitations of the study include a limited number of high-risk individuals (women and non-agricultural workers comprised the bulk of the population) and the potential for recall bias due to the retrospective nature of the information on exposure. For example, as bolis are packaged in small discrete packets while water is carried in various-sized, refillable containers it is likely more difficult for workers to recall accurately the volume of water consumed as compared to the number of bolis. Workers incorrectly estimating water consumption has been reported by other authors (Jennifer Crowe, personal communication) and may help explain the lack of association seen with water consumption.

A second case-control study was conducted in the Guanacaste region of Costa Rica by the Costa Rican Health Care and Social Security System [21]. Cases (n=192) were patients aged 18-59 with a diagnosis of CKD during 2005-2011 based on two consecutive measurements of eGFR<60 3 months apart. Controls (n=317) were patients who were determined not to have CKD as a result of normal renal function tests. Controls were matched to cases based on sex and age. Eighteen percent of cases and 4% of controls were persons of Nicaraguan nationality living in Costa Rica, which was also adjusted for in the analysis. Results of the study indicated that being an agricultural day laborer (peón agrícola), working in the sugarcane industry, working between 10 AM – 2 PM, and greater use of anti-inflammatory pain medications (AINES/aspirin) were associated with greater prevalence of CKD.

Additionally, three prospective cohort studies have been conducted in Nicaragua and El Salvador; these studies were the first in the region where workers were assessed at more than one time point and changes over time could be assessed. The first study was conducted at a sugarcane company in northwestern Nicaragua among 284 workers in 7 job tasks [8, 22]. Blood and urine samples were collected prior to being hired for the harvest and near the end of the harvest. A questionnaire was administered including questions on work history, symptoms, medications, quantity of water and number of bolis typically consumed at work. Both serum creatinine and urine biomarkers of kidney injury were measured and compared across job and time. Factory workers were the reference group for all analyses. Analyses were adjusted for sex, age, and duration of employment. From beginning to late harvest, eGFR decreased a further 5-9 mL/min/1.73 m2 in seed cutters, irrigators, and cane cutters, as compared to factory workers [8]. These three jobs also reported drinking the most water per day. Cane cutters experienced the largest increases in NGAL and IL-18 relative to factory workers during the harvest [22]. Water consumption was unrelated to eGFR or biomarker measures, but cane cutters who consumed a greater number of bolis had both a smaller decline in eGFR and less of an increase in NGAL than cane cutters who consumed a smaller number. No association was seen for other job categories. The authors concluded that the greater decrement in eGFR and increases in biomarkers among field workers, particularly cane cutters, along with the protective effect of greater boli consumption, was most consistent with the HS/D hypothesis. While a strength of this study was the comparison of different jobs within the same industry that had different potential HS/D exposures and other potential risk factors, HS/D was not directly measured. Additional limitations included the fact that changes in eGFR were generally small and of uncertain clinical significance, and that a pre-employment screening program partially selected out workers with elevated creatinine [2]. As with the study by Raines et al [20], the apparent protective effect of greater boli consumption compared to water consumption could be due to misclassification.

Data analysis is ongoing for two additional prospective cohort studies. One was conducted among workers in a community setting in northwestern Nicaragua (Aurora Aragón, personal communication), and the second a component of the WE intervention underway at a sugarcane company in El Salvador (see *"WE program pilot intervention 2014-2015: Lessons learned"*, in this report).

Future considerations

Current evidence makes the following considerations of particular importance in ongoing and future work:

Water is the main element lost with sweating/dehydration and therefore should be an important component of a hydration program. Currently, there is insufficient information regarding the consumption of carbohydrate-electrolyte drinks to determine how they should be incorporated into a hydration program and it should be noted that these drinks typically contain fructose, which emerging animal data suggest may be linked to kidney damage in the context of dehydration [23].

Because of the nature of the exposure assessment (including collecting information on plausible potential confounders such as agrichemical exposure), case-control studies will generally be limited for assessing the HS/D hypothesis, although a valid job-exposure matrix that can broadly quantify various occupational exposures may be able to overcome this problem.

If studies are instead prospective cohort by design, then money and time are the main obstacles. The number of new diagnosed CKD cases that would develop each year is not sufficiently large to obviate the requirement for a very large number of study participants, substantial duration of follow-up, or both. Use of a strongly predictive intermediate marker would help address this problem. Advances are being made in this area (see working group report "*Exploring biomarkers for early evidence of abnormal kidney function*," in this report).

There are at least two strategies for collecting the necessary evidence through prospective cohort studies, which are not mutually exclusive. The first is to conduct one or two large studies, the second to conduct a number of smaller studies and then conduct a pooled or meta-analysis. The effectiveness of the latter strategy will be maximized if there is as much standardization as possible regarding methods, sample testing, and questionnaires.

If the disease is in fact of multifactorial etiology, incorporation of the assessment of other potential causal agents or conditions may help lessen the time needed to clarify the role of HS/D. The risk will likely be most evident among workers with both factors; if the interaction is a strong one, analyses that account for this interaction may be more powerful than those that ignore it.

The timing of biological measures must be considered. Circadian rhythm is well-known to affect cardiovascular responses and body core temperature. Diet [24] and muscle damage [25] can affect circulating creatinine levels in the body. Also, the recovery of renal responses (i.e., renal blood flow and GFR) following exercise can take anywhere between 1-2 hours to 24-48 hours depending on the variable of interest (i.e., proteinuria and muscle damage markers) and recovery conditions [26, 27]. Urinary protein excretion should be reported as a rate (i.e., ug/min) to correct for changes in urine concentration/output throughout the day [26].

Remaining questions for the HS/D hypothesis

As noted above, one of the difficulties of the HS/D hypothesis is the perception that many people around the world carry out strenuous work in conditions of high ambient temperature and with insufficient hydration. Simple seroprevalence studies in other regions in which conditions are similar but not currently identified with CKD epidemics would provide useful data. The question of "why here" is particularly relevant to other regions in which sugarcane production is an important industry. For example, sugarcane cutters in Brazil show decreases in eGFR and increases in serum creatinine across shift, yet CKD has not been reported as an important problem in this population [11]. However, this perhaps highlights the gap in understanding between acceptable kidney stress due to strenuous activity and sub-clinical indicators of kidney injury. Determining the prevalence of CKDnT in other settings and what factors might explain any differences would help provide more clarity on those factors that may be important in Central America. Further work is also needed to establish appropriate kidney biomarkers and normative ranges in order to differentiate a stress response from kidney injury or disease. This would clarify the clinical significance of measured changes in kidney biomarkers.

Summary

In sum, studies to date have used proxy or self-reported measures of HS/D and have mainly not been able to adjust for other potential risk factors for CKDnT that may be associated with these proxy measures. A natural next step in evaluating the HS/D hypothesis epidemiologically would be to take advances made in measuring HS/D and apply them in studies with longer-term follow-up. It is important to note that this discussion applies to the question of obtaining the evidence to decide whether or not HS/D is an important cause of CKDnT. Given the documented heat stress and strenuous work conditions, interventions to reduce HS/D based only on preliminary evidence or even regardless of its connection to CKDnT are appropriate and necessary.

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Does exposure to toxic metals have a role in the development of Mesoamerican Nephropathy (MeN)?

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Introduction

In this working paper we will examine the possible role of exposure to toxic metals in the development of a specific type of chronic kidney disease that have been given the name Mesoamerican nephropathy (MeN) (1). In spite of its name MeN possible affects persons in several parts of the world. Sometimes the MeN referred as chronic kidney disease of unknown cause (CKDu) chronic kidney disease non-traditional cause (CKTnt) or sugar cane nephropathy (2).

As starting point we will make reference to the classical review by Austin Bradford Hill in 1965 (3) on the issue of The Environment and Disease: Association or Causation? Subsequently we will make an attempt to apply these principals to what we now about exposure to toxic metals and renal effects in general and in particular to what we know from published reports concerning exposure to toxic metals and MeN. In fact these principles for judging on causality from Hill may well, as we see it, be useful for the evaluation of causality of MeN in general, and not only for metals.

Evidence of exposure to toxic metals and renal effects

A comprehensive review on this subject was published by Barregård and Elinder in the recently updated two volume textbook Handbook the Toxicology of Metals in 2014 (4) and overview was also given at the previous international meeting on Mesoamerican nephropathy (5). Chapters with detailed descriptions of the toxicity of a series of metals of interest in relation to human exposure and health are also available in Handbook on the Toxicology of Metals; Arsenic (6), cadmium (7), mercury (8) and lead (9). There is also easily available and updated information of what is known about human toxicity of these metal in UpToDate; (10-14).

Here we will shortly in tables summarize the following. Do we have information or knowledge on; Evidence of nephrotoxicity in humans, specific clinical and morphological findings in human nephrotoxicity, the existence of clear-cut evidence of nephrotoxicity in animal experiments, specific biochemical and/or morphological findings in animal nephrotoxicity, established dose-effect and dose response relations between exposure and renal effects in humans, the possibility to use measurements in blood and or urine (biological monitoring) to assess exposure and the existence of established dose-effect and dose response relations between results from biological monitoring and renal effects in humans for five non-essential metals; arsenic, cadmium, lead, lithium and mercury.

We will review the evidence of significant exposure to these metals in MeN (CKDu) endemic areas from environmental measurements, from biological measurements in blood and/or urine. Next we will examine to what extent the clinical and renal morphology findings in cases with CKD in endemic areas agree with those from confirmed cases of renal toxicity from exposure to metals. Are they similar or not?

We will use the following crude classification of associations; - none, + limited or weak, ++ yes and +++ strong.

Arsenic; Albeit inorganic arsenic overall is highly toxic to humans, a classical poison with an acute lethal dose of about 1-3 mg/kg and with a series of chronic toxic effects there are remarkably few renal ones mentioned in extensive textbooks and reviews(6). There are merely a few cross-sectional studies on associations between exposure to arsenic in drinking water and proteinuria, but this may be due

Table 1. Metal exposure and renal effects: Agreement between morphology and renal toxicity from exposure to metals.

Metal	Arsenic	Cadmium	Lead	Lithium	Mercury
Evidence of nephrotoxicity in humans	+	+++	++	+++	+++
Specific clinical and morphological findings in human nephrotoxicity	-	+++	+	++	++
Specific biochemical and/or morphological findings in animal nephrotoxicity	-	+++	++	++	++
Established dose-effect and dose response relations between exposure and **renal effects** in humans	-	+++	-	+	++
The possibility to use measurements in blood and or urine (biological monitoring) to assess exposure	+	+++	+++	+++	+++
The existence of established dose-effect and dose response relations between results from biological monitoring and renal effects in humans.	-	+++	-	++	++

to confounding from other exposures and in particular reversed causality; i.e. proteinuria, which in turn is signalling glomerular damage, brings about increased urinary excretion of arsenic. One particular problem with arsenic is the use (or misuse) of measurements of arsenic in urine to assess exposure and eliminating the pronounced effect from intake of seafood (10). Normal levels of arsenic in urine, in the order of 5-50 ug/l, may become increased more than 20-times after ingestion of seafood contain 'fish arsenic' (i.e. arsenobetaine). To avoid this effects of seafood a strict fish- and shellfish free diet must be kept or the urine analysis specified in different forms of arsenic, origin from exposure to inorganic or fish arsenic (6).

Cadmium; Renal effects from exposure to cadmium are well established in humans as well as in animals. The earliest effects from cadmium are typical with signs of renal tubular dysfunction with increased urinary excretion of tubular proteins and enzymes. The metabolism of cadmium and its accumulation in the kidneys due to the formation of a specific metal binding protein – metallothionein – have been delineated (7). Later glomerular effects may come with a drop in the glomerular function and an increased risk for renal stones. Measurements of cadmium in blood and urine are useful assessing recent as well as long-term exposure. Dose-response curves for cadmium in urine and renal effects from a large number of studies in humans are in grossly good agreement and form the basis for environmental and occupational threshold values (7, 12). Morphological findings in kidneys from human cases and animals with renal toxicity agree well, tubular damage with interstitial inflammation and fibrosis with secondary glomerular damage, are not specific.

Lead; Lead is a classical nephrotoxic agent and lead nephropathy has been described in medical report for more than 100 years. However, when the evidence for nephrotoxicity from lead is thoroughly scrutinized the evidence is not that impressive and hard to replicate in animal experiments(15). There is however one possibly pathognomonic finding in renal biopsies that can be seen as result of excessive exposure, and this is nuclear inclusion bodies with a high content of lead(16). However this does not translate in to renal damage but is more of a proof that excessive exposure, which often may cause other types of non-renal effects. The clinical and renal morphological descriptions of cases with diagnosed lead nephropathy are not very specific, but rather non-specific with slightly decreased glomerular filtration (lowered eGFR) and interstitial inflammation, secondary fibrosis and glomerular sclerosis(14). Thorough examination of lead exposed groups of adults with well-defined lead exposure have, in large, been unable to reveal more specific effects of the glomerular or tubular function. Measurements of lead in blood have been proven to be very useful in assessing exposure and different types of adverse health effects, but not renal ones. Lead in urine can also be used but is less stable and more difficult to use for assessment of exposure (9).

Lithium; Exposure to this metal is widespread from worldwide from the use of lithium in the treatment and prophylaxis of manic-depressive disorders. Typical daily doses of lithium to reach a therapeutic level in plasma of around 0,5-0,8 mmol/l is around 1,500 mg of lithium carbonate which contain 282 mg of lithium. Daily intake from food and water normally range from 0.6 to 3 mg/day. Drinking water in very lithium areas may reach concentrations of 500-1000 ug/l (17). During medication intake of lithium is increased with a factor of 100. Measurements of lithium in blood and urine can be used to assess intake from water. In individuals using drinking water rich in lithium (500-1000 ug/l) blood or plasma levels of lithium may reach levels in the order of 100 ug/l(18). This is far below the therapeutic range in plasma of 0.8 to 1.2 mmol/l (5,550-8,330 ug/l). The therapeutic range for lithium is narrow and symptoms and signs of lithium intoxication may appear at plasma levels exceeding 1.2 mmol/l and above 3 mmol/l they may become life threatening. Neurological symptoms and signs dominate, often polyuria with production diluted urine is seen and – in severe cases – EKG changes and risk for circular

Table 2. Likelihood of association with MeN (CKDu) and exposure to metals.

Likelihood of association with MeN (CKDu).	Arsenic	Cadmium	Lead	Lithium	Mercury
Evidence of significant **exposure** in MeN (CKDu) endemic areas from environmental measurements or biological measurements.	+	-	-	-	-
Clinical concordance between cases with CKD in endemic areas with of what has been reported from humans exposed to metals.	-	-	+	+	-
Renal pathology in concordance between cases with CKD in endemic areas with of what has been reported from humans exposed to metals.	-	+	+	-	-

collapse. Also in the therapeutic range lithium affects the renal handling of sodium and concentrating capacity of the kidneys, and decreased ability to concentrate the urine and polyuria is common during treatment with lithium. Whether long term use lithium may produce CKD has been long debated. Most patients on long-term treatment with lithium (decades!) will retain their renal function but some may eventually develop CKD and end stage renal disease, not always clear if caused by lithium or not. Major risk factors for nephrotoxicity appear to be the duration of lithium exposure, the cumulative dose, and advanced age(19). The degree of renal insufficiency is generally relatively mild, but may occasionally progress to end-stage renal disease (ESRD). Nevertheless renal biopsies from patients with long-term lithium treatment has been reported to display a certain type tubule-interstitial changes with microcyst formation in the tubulus (20). These tubular cysts, which are typically seen during lithium treatment, are comprised of glycogen containing vacuoles. Occasionally lithium treatment may also precipitate a nephrotic syndrome in certain susceptible individuals. We have not found any report suggesting that environmental or occupational exposure to lithium may cause any of the above mentioned renal effects.

Mercury; Exposure to inorganic mercury may cause early subtle tubular effects with increased urinary excretion tubular enzymes in groups of occupationally exposed workers, and occasionally, in individuals with very high exposure to inorganic mercury from various sources such as for example skin-lightning mercury containing moistures and creams, a nephrotic syndrome with heavy proteinuria. Renal biopsies in cases with mercury induced nephrotic syndrome often reveal glomerulonephritis of minimal change or membranous type. As a rule the nephrotic syndrome is reversible when exposure to the inadvertent exposure has ceased. Measurements of mercury in urine is useful in assessing exposure and in diagnosing cases of poisoning (21).

There is no robust data (without analytical problems or, in the case of mercury speciation problems) providing evidence of excessive exposure to toxic metals in MeN/CKDu endemic areas of Central America. The histopathological findings from renal biopsies so far presented from endemic areas do not resemble those seen in cases with classical cases of metal poisoning(22), although one could argue that non-specific sclerotic changes are seen also in cases with cadmium and lead nephropathy, thus one +. Clinically MeN is characterized by lowered eGFR and no, or limited, proteinuria. This is clearly different from cadmium and mercury, but weakly compatible with lead. Patients with MeN, working and living in hot climates, often report high daily intake of fluids sometimes exceeding 8 l/day. Albeit this has similarities with the polyuria commonly experienced by patients treated with lithium there are no data suggesting excessive exposure to lithium on Men/CKDu endemic populations. In addition the typical tubular cyst in patients under lithium treatment has not been reported in biopsies from patients in MeN/CKDu endemic areas.

In Sri Lanka it has been shown that people who live in disease endemic region may be exposed to arsenic, cadmium, and some other metals, through drinking water, food and tobacco to a greater extent than in people living in non-endemic regions (23, 24). However, the clinical picture and renal pathology is not compatible with metal poisoning.

Measurement of arsenic, cadmium and lead in biological media from populations with CKD of unknown cause in Central America has not shown potentially toxic levels of these metals, but in the normal range (25). Likewise the concentration of a series of potentially nephrotoxic metals, including arsenic, cadmium, lead and lithium has recently been measured in drinking water and urine from patients with and CKDu, and individuals without CKDu in CKD endemic and non-endemic areas of Sri Lanka. Overall the concentrations were low and water as well as in urine and there was nothing indicating a causative association between exposure to metals and CKDu (26).

Overall summary

When scrutinizing available knowledge on renal effects and exposure to toxic metals (arsenic, cadmium, lead, lithium and mercury) and information about exposure to these metals in MeN/CKDu endemic area, the clinical presentation and morphological findings, we conclude that it is unlikely that this epidemic is primarily caused by exposure to these metals.

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Chronic kidney disease of undetermined etiology and pesticide exposure: an update on recent data

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Introduction

For more than two decades, various regions of the world including Central America (1), Sri Lanka (2), India (3-4), and Egypt (5) have experienced an excess of chronic kidney disease unrelated to traditional causes as hypertension and diabetes. As such, it is often referred to "CKDu", for "undetermined etiology", as well as "MeN" for "Mesoamerican nephropathy" for the centroamerican and mexican epidemic. Since PAHO officially refers to the disease as "CKDnt", focusing on its "non traditional (nt)" causes (6), this term will be used hereafter and account for all three denominations unless specified otherwise. CKDnt emerges disproportionally in patients from often disadvantaged communities with the resulting psychosocial consequences; it is thus recognized as a serious public health problem that must be thoroughly addressed (1, 7 – 9).

Although the precise etiology of the epidemics remains unknown, it is generally well recognized that multiple causes are likely involved, with two main hypotheses being put forward. First, a striking male/female ratio of 3:1 or higher documented in Central America countries strongly suggests that the occurrence of CKDnt in this region is associated with an occupational exposure experienced primarily by men (1, 8, 10). In particular, strenuous agricultural work in hot climatic conditions, often in sugarcane plantations, leading to heat stress with repeated episodes of dehydration (and, hypothetically, rhabdomyolysis), combined with excessive consumption of NSAIDS to relieve muscular pain, have been suggested as important risk factors (1, 5, 8, 9, 11 – 14). Second, the gender disparity of CKDnt cases in Central America is also compatible with occupational exposure to pesticides, which are handled preferentially by men in this region. In El Salvador and Sri Lanka agrochemicals have been targeted by national policies (15, 16). Although in the first International Workshop on MeN such exposure was considered an unlikely cause of CKDnt based on regional data available prior to 2012 (8), this review is prompted by persisting concerns of scientists, policy makers and the general society raised by a series of recent publications that could shed new light on the issue. The current short paper thus aims to provide an update on the state of knowledge regarding this issue, and strictly focuses on articles published since 2012.

Approach followed

Much of this paper is based on an ongoing thorough retrospective literature review (manuscript in preparation) of original epidemiologic studies looking into chronic kidney disease and considering associations with pesticide exposure.[5] Briefly, data on geographical area where the study was conducted, study design and pop-

1. This review, carried out under the auspices of PAHO, is based on a manuscript in preparation that focuses on the scientific literature published since 2000 and is co-authored by M Valcke, ME Levasseur, L Revez, A Soares and C Wesseling, to be submitted in early 2016.

ulation, exposure assessment, case definition or outcome(s) and statistical methods used to examine potential associations between pesticides and CKD in general or end-stage renal disease (ESRD) were extracted. Reported results were qualitatively evaluated based on the validity of the studies and strength of associations.

Relevant recent evidence

A total of 16 peer-reviewed papers published since 2012 have formally examined pesticide (or so-called "agrochemical") exposure by some direct or indirect means, although often quite superficially (Table I). Overall, the evidence of a relation between pesticide exposure and CKDnt is not obvious based on negative or inconclusive results in quite few studies (17 - 22) for which the exposure assessments realized were, in general, limited. Except for Jayasumana *et al.* (23), Lebov *et al*. (24) and Raines *et al*. (25), the studies reviewed generally relied solely on questionnaire/interview data with qualitative questions such as "ever/never used pesticides?", or indirect, qualitative occupational characteristics such as "applicator, sprayer, preparing pesticide formulation". Besides, being mostly cross-sectional, the studies retrieved could not confirm the temporality of potential pesticide exposure within the work or residential history with regard to onset of CKDnt cases (e.g: 15, 25, 26).

Such limited exposure assessment may have resulted in important misclassification of exposure status that, if non-differential, may have biased the results towards the null with corresponding underestimation of the true risk. The participants were generally aware of the CKDnt epidemics in their region as well as the fact that it is thought to be associated, at least in part, with working in sugarcane plantations and corresponding pesticide use; thus over- reporting such potential exposure may have occurred. However, recall bias, when significant associations were measured, appear unlikely since most subjects involved in the reviewed studies did not even know the outcome of their kidney function tests when they were interviewed. Still, positive associations were obtained in some studies for farming or agricultural-related activities in general (10, 22, 25), which includes but is not limited to pesticide exposure, and certainly also involves strenuous workload at some level.

The lack of specific consideration for the likely confounding effect of such heavy workload in intense heat experiences in any kind of agricultural work but in particular cutting in sugarcane plantations, on the observed associations between CKD and pesticide exposure, is a critical issue that needs to be further examined. This would contribute to isolate and appreciate the true magnitude of the potential causal factor of pesticides to the "CKDnt/agricultural work" relation. It may contribute to further investigate surprising results such as the significant bivariate OR of CKDu with virtually every agricultural pesticide considered by Jayasumana *et al.* (23): organophosphates (OR=1.77 [95% CI 1.10-2.86]), paraquat (2.51 [1.56-4.04]), MCPA (1.80 [1.12-2.88]), bispyribac (2.00 [1.25-3.18]), carbofuran (1.47 [0.91-2.40]), mancozeb (1.94 [1.21-3.13]) and glyphosate (4.33 [2.66-7.05]). Among these, only paraquat is a known human nephrotoxicant, although some of the other agents have shown nephrotoxicity in animal models (27, 28). This Sri Lankan study observed an increased risk if the source of drinking water was a serving well (2.52 [1.12 – 5.7]) and a higher risk for abandoned wells (5.43 [2.88 – 10.26]), the latter with higher levels of glyphosate residues. This strong association is coherent with the fact that this herbicide has been hypothetically linked with ESRD, although in a very superficial caveat-full ecological study (29), is the most widely used in the disease endemic region and exhibs an amphoteric and zwitterion structure capable of chelating metals, including nephrotoxic ones (e.g. cadmium). Whether resulting from either an occupational exposure or not, the resulting glyphosate-metal complex would exhibit a half-life that is hundred fold higher than for individual substances (14). Besides, ingestion of water containing 0.1 ppb of glyphosate-based herbicide resulted in kidney damage in a two years follow-up rat model (30), whereas concentrations measured in the

Jayasumana *et al.* study were above 1 µg/l (23).

Dose-response patterns were observed among a cohort of more than 55 000 US licensed pesticide applicators, reported by Lebov *et al.* (24). Applicators hospitalized for any pesticide exposure had an elevated Cox proportional hazard ratios (HR) for ESRD (3.05 [1.67, – 5.58]). Also, ESRD was related to the number of times medical assistance was sought due to pesticide exposure (max. HR 2.13 = [1.17 – 3.89], p_{trend} = 0.0384). Increased HR were also obtained for applicators exposed in the highest intensity-weighted lifetime exposure category as compared to non-users, and significant exposure-response trends were obtained, for the following pesticides: atrazine (1.52 [1.11 – 2.09], p_{trend} = 0.008), paraquat (2.15 [1.11 – 4.15], p_{trend} = 0.016), pendimethalin (HR = 2.13 [1.2 – 3.78], p_{trend} = 0.0057), alachlor (HR = 1.51 [1.08-2.13], p_{trend} = 0.015), metolachlor (HR = 1.53 [1.08 – 2.18], p_{trend} = 0.0084) and permethrin (2 [1.08 – 3.68], p_{trend} = 0.031). There were associations without exposure – response trend for petroleum oil and imazethapyr, and non-significantly increased HR (>1.6) for coumaphos, parathion, phorate, aldicarb, chlordane and metalaxyl. No increased risks were observed for the remaining 25 pesticides.

Siddharth et al., (3, 4), found higher organochlorine (OC) pesticide blood concentrations in urban CKD patients than in controls, and eGFR was significantly negatively correlated with hexachlorocyclohexane, aldrin and total OC pesticide blood concentrations. Associations were particularly strong among subjects with null Glutathione S-transferase (GST) genotypes - and hence lack of detoxifying enzymes - (4), which reduces the possibility of reverse causality, i.e. reduced kidney function and corresponding excretory capacity resulting in higher blood levels. In a cross-shift study in sugarcane cutters, García-Trabanino *et al.* (26) observed that ever using carbamate was a significant predictor of reduced eGFR in sugarcane cutters, whereas no association was observed for glyphosate, paraquat, 2-4 D, organophosphates, triazines, pyrethroids or captan. In Nicaraguan pesticide sprayers in a sugar mill, no significant changes in eGFR were observed over a harvesting season (19), and markers of early tubular kidney injury did not change over the harvest season (31). Finally, a study in three Salvadorian communities (10) reports that exposure to methyl-parathion in one of them, being suburban agricultural community adjacent to an abandoned warehouse agrochemicals, significantly increased CKD probability (OR 2.6 [1.24-5.45]), but the paper's methods section only refers to self-reported "contact with agrochemicals" without further characterization .

In view of Table I, there seem to be a tendency towards positive association between pesticide exposure and CKD in general being observed in recent studies outside Central America. A role of pesticides in the etiology of CKDnt can still be hypothesized physiopathologically in harsh working conditions, either due to exposure to highly concentrated renal-excreted toxins in situations of profuse sweating and low fluid intake, or increased intake due to greater consumption of contaminated drinking water or inhalation and dermal contact rates resulting from high cardio-respiratory rhythm and dermal vasodilatation. The lack of sound exposure assessment with only crude self-reported binary measures of ever exposure to pesticides, a very large and heterogeneous group of agents, and the lack of taking temporality into account in most studies hitherto performed is apparent. Along with continued characterization of the involved physiopathology, robust and consistent exposure assessment throughout the different parts of the world affected by CKDnt could inform on whether we are facing one global disease or region-specific diseases with similar renal outcomes. Not only workers with repeated occupational pesticide exposure but also low chronic environmental exposure in the general population should be studied in well-designed prospective studies that accurately accounts for potential confounders in order to shed further insight on possible causal factors of the disease, allowing the scientific community to better understand, and maybe either confirm or discard, a possible role of pesticides in CKDnt.

Conclusion

The results of this review do not allow firm conclusions on the role of pesticides in the etiology of CKDnt. However, despite frequent severe exposure misclassification with the resulting trend towards absence of risk, positive results have been obtained in several studies published in the more recent years, in particular those with better exposure assessments and stronger designs. To our view, this is sufficient to raise questions that should be further investigated before discarding any causative role of these chemicals known to be toxic to humans in variable conditions. Arguments in favor of the hypothesis of an etiological role of pesticides in the CKDnt epidemic include 1) CKDnt appears more frequently in agricultural populations, including women (32), in identified high-risk areas ;2) those areas all exhibit high pesticide usage, including some with likely nephrotoxic properties (6, 27, 28, 33); 3) a possible chelating effect of some pesticides, the prime candidate hypothesized in the literature as being glyphosate (14, 34), on nephrotoxic metals present in hard drinking water, which thus may accumulate more heavily in renal tissues. Arguments against pesticide as a cause include that 1) there are hundreds of different active ingredients of pesticides/agrochemicals, with distinct toxicities, that cannot really be grouped all together as if they were one single nephrotoxin, as proposed elsewhere (33), without generating a huge misclassification of exposure; 2) that in order to point out a single or limited number of pesticides as a significant contributing factor, a truly universal nephrotoxic pesticide with numerous men exposed would need to be identified; however, such identification has not occurred yet. Further investigations should focus on specific agrochemicals and use adequate exposure measures within a framework that considers a wide range of public health determinants and corresponding actions. Indeed, causal hypotheses about CKDnt are not necessarily mutually exclusive, and require equal attention. Therefore, future studies should focus not only on environmental determinants (e.g. use of agrochemicals, temperature) but also on poverty conditions that could interact with any other etiologic factor including toxic exposure. This could bring out regional discrepancies/similarities of CKDnt, clarify the disease's causes and contribute to the implementation of measures that will help reduce its serious public health burden in the affected countries.

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Table 1: Studies of interest for exploring the role of pesticides in the etiology of CKD and ESRD published in 2012 and after.

Reference & country	General Method	Outcome[a)]	Association main findings[b)]
Payan-Renteria et al., 2012 Mexico	• Cross-sectional study based on 25 exposed male farmworkers and 21 unexposed workers • Exposure assessment: the exposed group had sprayed pesticides last season • Spearman correlations and more	SCr and serum uric acid	Negative, but unclear description of the statistical method, i.e. suggest cluster multivariate analysis but do not present the corresponding results.
Laux et al., 2012 Nicaragua	• Community-based cross-sectional survey on 267 adults (120 ♂) • Exposure assessment: face to face questionnaire - "Work with pesticides 'yes/no'" • Univariate and multivariate logistic regressions	Proteinuria adjusted for DB and HT	Negative
Siddharth et al., 2012 India	• Hospital-based case-control in 246 adults (128♂), incl. 150 cases (77♂) • Exposure assessment: organochlorine pesticide residue levels in blood • Spearman correlation; 2-way ANOVA with Bonferroni analysis	CKD	Weak positive correlations with some organochlorine pesticides
Jayatilake et al., 2013 Sri Lanka	• Cross-sectional population-based prevalence survey in 4777 adults (1991 ♂) with case-control analyses (733 cases, 520 ♂) • Exposure assessment: face to face questionnaire (protection from agrichemicals, all subjects) + urinary biomonitoring (57 CKDu patients) • Logistic regressions of risk factors, adjusted for age and sex	CKD and CKDu	Negative, but hardly interpretable

Reference & country	General Method	Outcome[a)]	Association main findings[b)]
Siddharth et al., 2014 India	• Hospital-based case-control in 540 patients (270 cases, 140 ♂) • Exposure assessment: biomonitoring of organo-chlorine (OC) pesticide residues in blood; glutathi-one S-transferase (GST) genotyping • Mann-Whitney U-test; multivariate logistic regres-sions	CKDu	Strong positive association with HCH, endosulfan, DDT and total OCs, especially in presence of GSTM(-) / GSTT(-) genotype, discarding in part the possibility of reverse causality.
Mejia et al., 2014 El Salvador	• Descriptive survey of 42 CKDu male farmer cases • Exposure assessment: face to face questionnaire - past exposures conditions to various types of pesticides • Descriptive statistics only	CKDu	Not measurable
Raines et al., 2014 Nicaragua	• Cross-sectional population-based survey (424 adults, 166 ♂); nested case-control analysis • Exposure assessment: researcher-administered questionnaire - detailed conditions and frequen-cies of past exposure • Uni- and multivariate analyses	eGFR	Weak positive, non significant association with lifetime days working with pesticide (univariate analysis) Significant association with nondeliberate pesticide inhalation (multivariate analysis)
Vela et al., 2014 El Salvador	• Descriptive survey in 223 age ³ 15 (111 ♂) • Exposure assessment: face to face questionnaire - “contact with agrichemicals ‘yes/no’” • No statistical testing	CKD	Not measurable
Orantes et al., 2014 El Salvador	• Cross-sectional population-based survey in 2388 adults (876 ♂) • Exposure assessment: face to face questionnaire « general/specific contact with agrichemicals” • Uni- and multivariate analyses	CKD	Positive association, with methyl-parathion only, in one of 3 communities. No information on exposure assessment.

Reference & country	General Method	Outcome[a)]	Association main findings[b)]
Herrera et al., 2014 El Salvador	• Case series (46 individuals age 18-59, incl. 36 ♂) • Exposure assessment: personal interview by sociologist with tailored questionnaire - Farming, contact with agrichemicals • Descriptive statistics only	CKD	Not measurable
Laws et al., 2015 and Laws et al., 2016 Nicaragua	• Cohort of 284 sugarcane workers (251♂), incl. agrochemical applicators • Exposure assessment: Field worker vs non-field worker; agrichemical applicator vs factory worker • t-tests, paired t-test, multivariate regressions, pre-post harvesting season	SCr, eGFR, proteinuria, tubular markers of kidney injury	Negative
Orantes et al., 2015 El Salvador	• Cross-sectional population-based survey in 1412 women aged ³ 18 • Exposure assessment: face to face questionnaire - agricultural worker, contact with general/specific agrichemicals • Descriptive statistics only	CKD and CKDnt	Not measurable
García-Trabanino et al., 2015 El Salvador	• Cross-sectional study in 189 sugarcane cutters (168 ♂) • Exposure assessment: face to face questionnaire - general and specific pesticide use ever • Logistic regressions	eGFR adjusted for HT	Positive association, with "ever used carbamate"
Jayasumana et al., 2015 Sri Lanka	• Case-control in 305 adults (187 ♂), incl. 125 cases (89♂) • Exposure assessment: face to face questionnaire detailing pesticide use up to 10 years back in time; drinking from serving wells and abandoned wells; analyses of glyphosate, metals, and hardness related parameters in water from serving and abandoned wells • Bi- and multivariate logistic regression	CKDu	Strong positive associations in bivariate (exposure to multiple specific pesticides) and multivariate analyses (drinking well water contaminated with pesticides, applying pesticide and use of glyphosate). Some dose-response pattern

Reference & country	General Method	Outcome[a)]	Association main findings[b)]
Rango et al. 2015 Sri Lanka	• Cross-sectional study in 109 adults and 25 children aged 10-<18. 82♂. • Exposure assessment: Concentration of As, Cd, Pb, Mo and U in urine. Household survey data on reported past pesticide use • Logit regressions	Albumin / creatinine ratio	Use of herbicides significantly higher in regions of endemic CKDu.
Lebov et al., 2015 USA	• Cohort of 55 580 licensed pesticide applicators (320 ESRD) • Exposure assessment: self-administered questionnaire regarding past use of 39 specific pesticides, accounting for a 5-years post enrolment lag time (to prevent healthy worker effect). Take-home questionnaire (n=24 565, 130 ESRD cases) for additional pesticide information • Cox proportional hazards models, adjusted for age and state; sensitivity analyses	ESRD	Strong positive association for medical assistance due to pesticide exposure; significant exposure response trends for intensity-weighted lifetime use of alachlor, atrazine, metolachlor, paraquat, pendimethalin, and permethrin.

Abbreviations: CKD, chronic kidney disease; DB, diabetes; eGFR, glomerular filtration rate; ESRD, end-stage renal disease; GST, glutathione-S-transferase; HT, hypertension; SCr, serum creatinine
a) CKD name as used by the authors (i.e. “CKD”, “CKDnt” or “CKDu”)
b) Association between the outcome indicated in the previous column and pesticide exposure as assessed in the study.

Proposed mechanisms for chronic kidney disease of uncertain etiology observed in Central America (Mesoamerican Nephropathy)

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Summary

A wide variety of etiologies have been proposed to explain the cause of Mesoamerican Nephropathy in Central America, including exposure to herbicides, pesticides, heavy metals (cadmium, arsenic, lead), toxins *(Aristolochia*), drugs (NSAIDs), infections (Leptospirosis, Hanta virus), metabolic causes (hypokalemia, hyperuricemia), and the effects of strenuous physical labor in the presences of heat stress and recurrent dehydration.

Recent findings support the hypothesis of cyclic daily uricosuria induced by heat stress and strenuous work as a plausible cause. Serum uric acid levels rise during the workday due to the increased release of substrate (purines) as a product of the intense muscle activity associated with strenuous labor and heat stress, leading to uricosuria. Simultaneously, physical activity generates endogenous heat, which adds up to the high environmental heat stress, increasing body core temperature. A transient state of volume depletion ensues, producing a fall in kidney perfusion and high demands on tubular reabsorption, with the consequent activation of several compensatory mechanisms (systemic vasopressin and local activation of the aldose reductase-fructokinase pathway in the renal tubule). Then, uricosuria in the concentrated and acidified urine leads to the formation of urate crystals.

As a result, the combination of the effects of low kidney perfusion, high tubular reabsorption demands, high urine uric acid with the presence of urate crystals, and vasopressin effects, could be producing daily, recurrent kidney damage that accumulates over time. This proposed mechanism: a) is supported by the recently published evidence, b) matches the histological lesions, and d) explains the clinical features of the disease, including the dysuria often reported by patients (passing of sandy urine).

This hypothesis opens the way for clinical trials focused on the use of drugs blocking the described pathways, possibly leading to treatment options in early stages, and ways to prevent the disease from developing in high-risk populations.

Main Text

The majority of patients with Mesoamerican nephropathy (MeN)[1-3] are male, working manually outdoors in hot tropical environments.[4-7] Apart from the occasionally reported dysuria, patients are mostly asymptomatic, typically presenting low-grade proteinuria (< 300 mg/day) and elevated serum creatinine. Hypokalemia and hyperuricemia are common. Blood pressure is normal or mildly elevated, and diabetes is absent. Some have crystalluria with dihydrate urate crystals and occasional subjects have microhematuria.[8] Kidney biopsies show chronic tubulointerstitial fibrosis with inflammation, often with ischemic changes and glomerulosclerosis.[9]

On the Etiology of Mesoamerican Nephropathy

Chronic tubulointerstitial disease may have multiple etiologies and has led to several potential hypotheses for what might be causing the epidemic (Table 1).[1,2,8] We will briefly discuss the major hypotheses.

Herbicides and Other Pesticides. The initial observation that CKD was common in agricultural workers led to the hypothesis that it might relate to exposure to herbicides (such as glyphosate and 2,4-D) or insecticides (such as chlorpyrifos and cypermethrin).[10,11] Glyphosate ingestion can be associated with acute kidney injury (AKI), and has been linked to a similar epidemic in Sri Lanka.[12] Since glyphosate is a chelating compound that forms complex molecules with metals present in hard water, when filtered through the kidney these molecules could cause damage. However, in Mesoamerica a primary role for agrichemicals seems unlikely. First, because workers at high altitude have a lower frequency of disease than those working at low altitude, despite similar pesticide exposure.[6,13] Second, studies of sugarcane workers show that cutters, not agrichemical sprayers, have the greatest risk [14,15]. Epidemiological studies of the general population also do not show an association with pesticides.[5] Furthermore, the observation that MeN also occurs in other occupations is not consistent with a pesticide mechanism. Finally, the toxicity of most agrichemicals involves neurological, respiratory, hepatic, and gastrointestinal signs, symptoms and syndromes, which are absent from the clinical presentation of MeN.

Heavy Metals and Toxins. Heavy metal poisoning from contaminated ground water has also been proposed, and at least one study has suggested cadmium toxicity may be involved in the CKD epidemic occurring in Sri Lanka.[12] Cadmium was the cause of a major outbreak of kidney disease in the early 20th century in the Jinzu River Basin, Toyama Prefecture, Japan, due to contamination from a mine.[16] However, the disease (itai-itai) presented more as a Fanconi syndrome with severe hypophosphatemia and a vitamin D-resistant rickets. Nevertheless, cadmium poisoning has been associated with hypertension and hyperuricemia,[17] possibly due to stimulation of xanthine oxidase by cadmium.[18] Low grade cadmium nephrotoxicity is still possible, as some studies suggest chronic toxicity is associated with elevated urinary biomarkers of tubular damage and a slow decline in kidney function over time,[19] although a source for a hypothetical broad cadmium contamination throughout the Mesoamerican region, affecting specifically male workers, has not yet been determined.

Inorganic arsenic species may also be potentially nephrotoxic and have been linked with proteinuria,[20,21] biomarkers of kidney injury,[22] and hyperuricemia.[23] However, arsenic poisoning is also associated with many other findings not present in MEN patients, such as hyperkeratosis on the palms and soles, leukonychia striata (Mee's nail lines), liver and gastrointestinal dysfunction.

Silica exposure, which is released from burning sugarcane, has also been suggested as a potential mechanism to explain the epidemic. Some studies suggest that individuals with high silica exposure, such as those working in construction or agriculture, have a higher frequency of CKD.[24] However, inhaled silica is usually associated with pulmonary symptoms and silicosis, which does not appear to be a usual finding in MeN patients.

Chronic lead toxicity is also possible, as it can be associated with CKD and hyperuricemia,[25-27] and can induce and accelerate tubulointerstitial disease,[28] but it is difficult to explain why it would occur primarily in the men working in the fields, as opposed to the general population.

Aristolochic acid. Accidental ingestion of plants containing aristolochic acid, a carcinogenic compound, produces a rapidly progressive chronic tubulointerstitial disease (aristolochic acid associated nephropathy) and is the cause of the Balkan Endemic Nephropathy and the Chinese Herbs Nephropathy.[29] Kidney biopsies generally show very little inflammation, which might appear to distinguish this from MeN, where focal inflammation is common. However, recent studies suggest that the lack of inflammation in aristolochic acid nephropathy is because biopsies are often collected in the late phase of the disease, and some studies suggest that its early renal injury is indeed associated with a pronounced inflammatory infiltrate.[30] Nevertheless, it seems unlikely that such a large, specific population would be exposed to this toxin.

Nonsteroidal agents. A potential iatrogenic cause is the frequent use of nonsteroidal anti-inflammatory analgesics (NSAIDs), a well-known cause of AKI, especially in the setting of volume depletion. NSAIDs, which are widely available, are commonly taken with and without prescription by workers for the aches and muscle pains they suffer from the demands of their work. The possibility that chronic use of NSAIDs may be an aggravating factor in the CKD epidemic seems plausible.[10] It is known that recurrent analgesic use (primarily compounds containing paracetamol, but NSAIDs may fall into this category as well) can result in chronic tubulointerstitial disease, occasionally with papillary necrosis, [31] a feature not observed in the MeN biopsies.

Metabolic Causes. Chronic hypokalemia is common in patients with MeN, possibly induced by chronic volume depletion. Chronic hypokalemia is known to cause tubulointerstitial fibrosis, in part by stimulating intrarenal angiotensin and endothelin production.[32] Subjects may also develop nephrogenic diabetes insipidus, and over time may show a loss of kidney function. Also, dehydration can be a source of volume depletion. Another common metabolic finding in subjects with MeN is hyperuricemia.[13] Hyperuricemia has been shown experimentally to cause both glomerulosclerosis and tubulointerstitial disease.[33-35] The role of uric acid in MeN is discussed in more detail below.

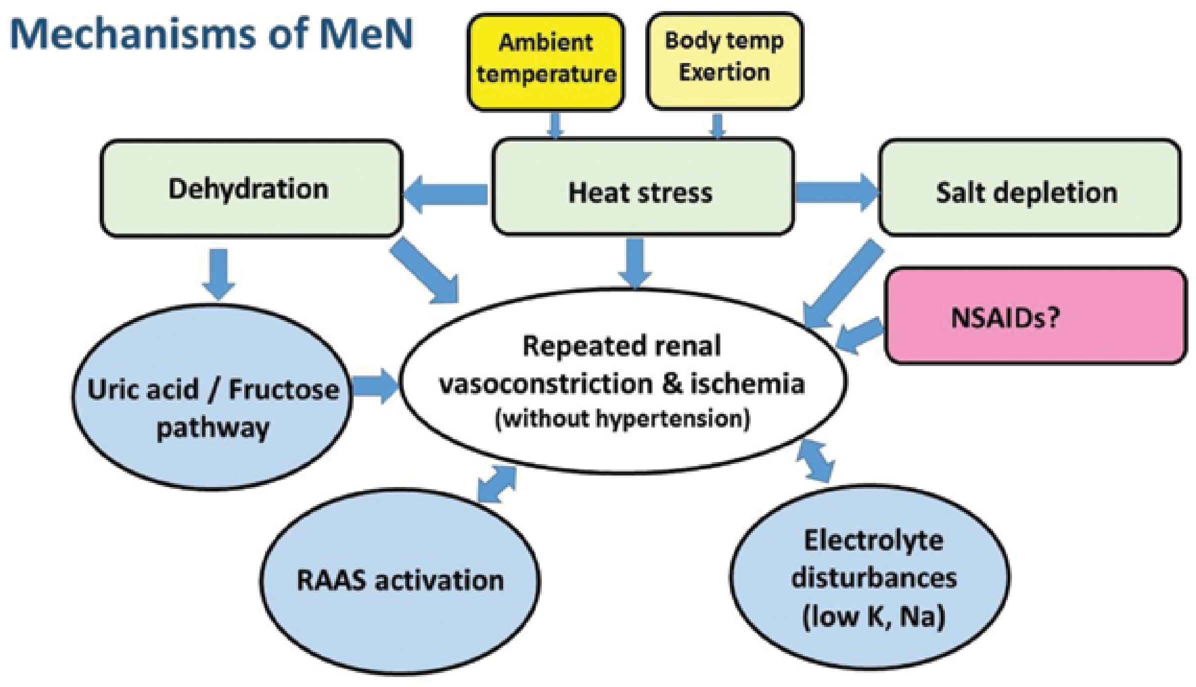
Infectious causes. Leptospirosis causes acute interstitial nephritis, often with fevers, conjunctivitis, muscle pains, and liver dysfunction, and is passed by skin exposure to rodent urine, a frequent plague in sugarcane fields. The possibility that severe or recurrent leptospirosis may lead to CKD has been entertained, but the lack of other features (liver disease, meningitis, etc.) makes this possibility less likely.[36] Likewise, while some Hanta viral infections may cause acute or chronic tubulointerstitial disease, no specific pathogen has been identified in these patients to date.

The Role of Dehydration and Heat Stress as a Cause of Mesoamerican Nephropathy

A common finding in patients with MeN is a history of working in hot environment where they are at risk for recurrent dehydration [13,37-39]. Some studies show that heat indices cross into the unsafe zone, defined by the Occupational Safety and Health Administration, by midmorning on a typical work day.[38] Workers not uncommonly develop signs of dehydration during the workday, as noted by symptoms (lightheaded, fainting) and signs (urinary concentration with a rise in urine osmolarity).[13,37-39]

Recurrent heat stress and dehydration may promote kidney damage via several mechanisms. First, sugarcane workers are prone to developing subclinical rhabdomyolysis.[40] While frank rhabdomyolysis is a classic cause of AKI, there is concern that recurrent subclinical rhabdomyolysis might also result in repeated and subtle damage to the kidney over time. Second, dehydration (loss of water greater than salt) is known to stimulate both the aldose reductase and vasopressin systems. There is evidence that chronic vasopressin stimulation may induce and accelerate CKD.[41] Furthermore, we found that activation of the aldose reductase-fructokinase enzymes in the proximal tubule of chronically dehydrated mice also develop CKD with tubulointerstitial fibrosis.[42] Finally, we recently identified the presence of urate crystalluria in sugarcane workers in El Salvador that approach levels similar to what is observed in the tumor lysis syndrome.[8] Thus, we have hypothesized that dehydration and/or subclinical rhabdomyolysis might lead to a rapid rise in serum uric acid and uricosuria, crystallizing in the acidic, concentrated urine.[8] In turn, crystals might induce local injury via binding to toll-like receptors or other mechanisms.[43,44] It is interesting that many sugarcane workers complain of dysuria, possibly a symptom of passing sand in their urine, locally referred to as chistata in Nicaragua and mal de orín in El

Figure 1. Proposed mechanism of chronic kidney injury in Mesoamerican nephropathy.



Salvador.[13,45] As a result, the combination of the effects of low kidney perfusion, high tubular reabsorption demands, urine urate crystals, and vasopressin effects could be producing kidney damage on a daily basis. Figure 1 presents the proposed mechanism for Mesoamerican nephropathy.

In summary, while the etiology of the epidemic of CKD in Central America remains unknown, the strongest evidence to date suggests that heat stress and recurrent dehydration play an important role, if not the dominant mechanism, in the development of MeN (Figure 1). This hypothesis opens the way for clinical trials focused on the use of drugs blocking the described pathways, possibly leading to treatment options in early stages, and ways to prevent the disease from developing in high-risk populations. Currently there is a major ongoing study to determine if improved hydration and proper rest in shady spots can reduce the development of CKD. Results of this study might provide key insights into how to reverse the epidemic and provide better health for those living in the region.

Table 1. Proposed Causes of Mesoamerican Nephropathy

Agrichemicals and Pesticides

Glyphosate (herbicide, metal chelator)
2,4-D (herbicide 2,4-dichlorophenoxyacetic acid and dioxin)
Chlorpyrifos (insecticide, a cholinesterase inhibitor)
Cypermethrin (insecticide, a nerve so-

dium channel modulator)
Paraquat (herbicide, reactive oxygen species => acute tubular necrosis)

Heavy metal and toxin exposure
Cadmium
Arsenic
Lead
Silica (from burning of sugarcane)
Aristolochic acid
Nonsteroidal agents (iatrogenic)

Metabolic Causes
Hypokalemia
Hyperuricemia

Infectious Causes
Leptospirosis
Hanta virus

Recurrent Dehydration and Heat Stress
Subclinical rhabdomyolysis
Dehydration with stimulation of vasopressin
Dehydration with activation of aldose reductase and fructokinase in the renal tubule
Uricosuria
Heat stroke

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Worker's Health and Efficiency Program – Lessons learned from a pilot intervention in El Salvador

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Rational for the study

We undertook an intervention study designed to prevent heat stress and dehydration among sugarcane cutters of a mill in El Salvador as a means to improve working conditions and to prevent CKD. Since sugar cane cutting is piecework, measures of maintaining or increasing productivity was a key part of the intervention.

The study design has three phases: Phase 1 - a pilot study to examine feasibility by field-testing each of the study elements; Phase 2 - an expansion to a sufficiently large population to examine feasibility and cost of a large-scale intervention as well as examine the effectiveness of the intervention in preventing heat stress and dehydration; Phase 3 - an expansion of the intervention beyond a single mill to demonstrate generalizability of the intervention. We are reporting on the feasibility studied in the pilot effort.

Methods

Study population:

Two groups (cutting fronts), cutting for Ingenio El Angel (the mill), were selected to take part in the intervention. We had had an earlier positive experience working with these two fronts (García-Trabanino et al 2015)[6] which represented two distinct environments; the coastal area at sea level (coastlands) and an inland area at 350-450 masl altitude (inlands).

The intervention: The intervention adapted OSHA's Water.Rest.Shade program in conjunction with efficiency training.

- A rest schedule was developed adapted from the US Army Research on Environmental Health (USARIEM) Heat Strain Decision Aid[7], modified for feasibility in this work setting.
- All breaks took place in the shade of a portable canopy built by the mill. Mill staff managed the Canopies moving them with the cane cutting teams throughout each workday.
- Potable water was provided by the mill, delivered daily by water truck to the field.
  - » The water was stored in 40 Liter coolers under each shade canopy.
  - » Each worker was supplied with a 3 Liter backpack-mounted bladder with connected flexible tube and mouthpiece from CamelBak® to permit continuous hydration. The CamelBaks were refilled at rest breaks with water from the cooler. Workers were urged to continue rehydration while returning to their community.

Efficiency training was conducted by two experienced Australian cane-cutting experts. It consisted of two parts:

1. A new design of the machete improved the ergonomics of repetitive movement of cutting cane, and

2. Fewer rows cut to reduce lateral carrying distance and consequently metabolic load.

Data collection: At a meeting before the harvest began, the study design and purpose was explained. At baseline all volunteers provided their signed informed consent for the following:

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2. Laurie Blanchard, USARIEM – personal communication.

- Blood and urine samples on four sampling days [pre- and post-shift at baseline, immediately before, during and at the end of the intervention]
- Urine samples pre-post-shift every second week [8 additional times]
Blood pressure, heart rate and weight
- Baseline questionnaire on a) socio-demographics, b) past and present work history, c) use of tobacco, alcohol and recreational drugs, d) general health and medications, e) family history of CKD and f) past and present symptoms of heat stress and dehydration.
- Brief questionnaires every second week on heat stress or dehydration symptoms, estimated total fluid ingestion, use of rest breaks and shade [12 times]
- A sub-study of 10-11 who wore heart rate monitors and accelerometers for 7 days to estimate workload.

Microscopy, specific gravity by microscopy and dip-stick of urine were done in the field and hemogram was performed the same day. All other samples were shipped to Sweden and analyzed in an accredited laboratory in one single run to avoid variability. Weather information and Wet Bulb Globe Temperature (WBGT) was measured continuously on a daily basis using a QUESTemp® 34.

Lessons learned
Preparations

Study Objectives: The pilot study was designed to test the intervention, to assure that participants would volunteer, and to test data collection in the field. Sample size was determined to test study and intervention feasibility and acceptance rather than to achieve an effect size for significance testing of intervention effectiveness.

The Protocol: Overall, we tried to do too much. We want to emphasize that each piece of data collection should be specifically matched to a study question to justify its inclusion to limit data collection and reduce risk of error.

Concerning the individual components we learned:

- Blood and urine samples were successfully collected at beginning and end of shift.
  - There were some nervous moments in making sure that we had sufficient and appropriate coolers to protect the samples to transport to the laboratory to be frozen and shipped.
  - The general cooperation of all participants in sample collection justified the time taken to clearly explain what we needed and why.
- Urine analysis in the field worked quite well and we are confident that this will prove the same next year. The key is identifying and hiring qualified and committed research technicians to carry out this work responsibly.
- Collection of weight and heart rate before work started was reasonably successful. Baseline measurement of BP was possible with the requisite 5-minute rest period, but this could not be done successfully in the field before a regular working day. We will likely not include BP after baseline in the future. Body weight after baseline, similarly will also not be considered next year since there are to many errors due to water and food intake in an uncontrolled environment.
- Our baseline questionnaire worked well but was too long. We learned about some important confusions and ambiguities (e.g., family, income) as well as difficulties related to certain time-frames (i.e. "During the last three weeks, have you...") that made this pilot effort all the more valuable. We plan to correct these areas of confusion, better target questions on some items and shorten the questionnaires.
- To our pleasant surprise the sub-study of workload worked out quite well and cooperation was excellent. We will try this again in the next zafra selecting participants who represented a range of work production as well as trying some improved technology for heart rate monitoring.
- We determined it necessary to send the

frozen samples to a collaborating laboratory in Sweden. While this was less than ideal in terms of efficiency the process ultimately went smoothly and all samples were received and logged without problem. The complete laboratory data are just now becoming available to us.

We wish to offer the following general advice about developing a protocol for such a field study. We conclude a final study protocol.

- Has to be decided upon at least three months before the start of the study to allow all stakeholders to make appropriate preparations and provide sufficient time for IRB-related delays.
- Should be translated into a detailed to-do list and by counting backwards appropriate deadlines should be assigned to all items with a substantial safety-margin. Err on the side of too much detail. It is almost impossible to overthink what needs to be planned for.
- Planning ahead is especially important for all types of equipment that cannot be bought or rented in the country but has to be imported.
- Items requiring engagement of multiple stakeholders and other complex processes should be given priority.

Health Problems that Arise: A plan on how to report results to workers and handle participants with possible health problems should be developed beforehand. Informing local healthcare providers and reaching agreements on referrals is important. While we made sure to make such plans, we found that there were barriers to easy access to necessary health care.

Gaining Participation: Reaching out and starting a sufficient dialogue to potential participants before the study starts is of utmost importance. This was not as straight-forward as we had hoped it would be. In our pilot we had to withdraw from one group due to security concerns as well as a lack of participation stemming primarily from a failure to find the best spokesperson(s) to communicate effectively with the target population.

Despite this failure with this second group we continued to engage with that group. By the end of the zafra we believe we successfully addressed the miscommunication and participants asked to be included in the end-zafra measurements as well as volunteered interest in being part of the full study in the following year.

Risk management

El Salvador is a violent and partly unsafe environment in which to conduct field studies. Its history of violence and exploitation of workers makes it a difficult task to achieve goals due to many uncertainties and risks. We needed to arrange for a security escort to accompany our research team during each field visit. The identification, assessment, and prioritization of risks followed by a coordinated approach to reduce the probability and/or impact of unfortunate events is crucial to success. Building a team of local staff and continuous dialogue with partners, workers, the local community and security forces are a good approach.

Communication

A communication strategy should be developed on the basis of the needs of all parties. Written communication using email is highly recommended, even when importance seems small. Although the existing, complexities of work organization and relationships among personnel can be formally described to investigators all organizations include informal structures and power relationships. These are only revealed to outsiders as they become important. We learned that we needed to assume that everyone wants to be copied on everything, and that we needed to re-confirm everything at least once.

One of the more difficult tasks is effective communication with the workforce throughout the study. Unless we were careful, communication to the workforce occurred only in groups or through workforce leadership. We were able to address the problem with reasonable success by having our investigators in the field all day (sunrise to end of work) on regular occasions. We became known and workers were able to interact with us over the course of a workday.

Intervention roll-out

Intervention studies in work settings are not common. There is a very good reason for this. Hardly anyone likes change. For that reason alone, it was critical that we engaged participants at all levels from the earliest possible moment. Everyone was going to be impacted by the changes we were implementing. As we initiated our intervention we made certain to take a step back and allow the engineers, agronomists, cane-cutters and caporales take part in planning and decision-making. An intervention, especially on a larger scale, is costly, time-consuming and induces a great deal of uncertainty. To achieve the necessary long-term commitment to the change it is essential to establish a notion of ownership by all actors and a willingness to assume responsibility for the different components of the intervention. We had to be as clear as possible about the intended intervention, the objectives we had in mind and the need to fit these into the existing work practices and work environment. We cannot overemphasize the need to be flexible and open to different routes to achieve this. For example, we developed a Water.Rest.Shade schedule that was based on laboratory studies in a normal population in a temperate climate. The schedule design, while generally appropriate, did not fit as well as we had hoped to the work practices in the field. Open discussion with the key personnel resulted in an acceptable compromise, which was then implemented.

Data collection

Fieldwork is time-consuming and subject to a lot of potential errors. Developing a "fool-proof" plan while recognizing nothing is truly "fool-proof" is of utmost importance. The protocol must include detailed, step-by-step instructions that are developed for each process or measurement in the field. The lead theme should be "make it easy to do it right" sufficient that even an untrained assistant should be able to succeed.

Managing resources

The complex dynamics of a project such as the WE program, which was implemented in a short time frame and with participation of multiple local and foreign partners, require the establishment of a clear budget with ongoing discussions of flexible expenditure spending to avoid confusion, establish study constraints, and facilitate necessary adjustments as the project evolves. This way, the limitations of the study in regards to sample size, work team size, number of field visits, lab tests selection, etc., can be managed as effectively as possible.

Implications for future studies

We conclude that a pilot study in advance of any effort to implement a full-scale intervention study is invaluable. Had we attempted to implement a full-scale study from the beginning, the number of problems and complications that we confronted would likely have caused the effort to fail. There is no question that a pilot effort of this scale is costly, time consuming and delays the implementation of an intervention that is strongly believed to be necessary and appropriate. Nonetheless, in the interests of achieving broad acceptance and evidence sufficient to convince skeptics, we believe a pilot effort of some sort is essential. We still have the challenges ahead to carry out the expanded intervention study and to demonstrate intervention effectiveness. We are looking forward to those challenges.

One last comment that is particularly germane to the objectives of this workshop. Since these studies are costly and time-consuming, study populations are usually small. We believe it is important to start coordinating studies wherever possible and to share protocols and questionnaires to enable future pooled analysis of data within this field.

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2. Laurie Blanchard, USARIEM – personal communication.

Boston University School of Public Health: Studies of occupational and non-occupational risk factors for chronic kidney disease

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Introduction

The research group at the Boston University School of Public Health (BUSPH) has been investigating Mesoamerican Nephropathy (MeN) in Central America since 2008. Given that the disease likely has a multifactorial etiology, our broad research program includes multiple studies designed to investigate the role of occupational and non-occupational risk factors experienced along the lifespan. At birth, there may be important differences in susceptibility to such exposures, including genetics. During critical stages of physiological development through adolescence, factors such as diet, medication, and environmental exposures may play a role in disease and/or susceptibility. Finally, once old enough to join the workforce, occupational exposures play a key role in disease onset either directly or as modifiers of other risk factors. Importantly, though we are conducting multiple studies to investigate risk factors across the lifespan, these are not 'separate' studies but rather multiple components of a single research program. The common goal of our work is to identify the cause(s) of the epidemic to inform intervention studies and minimize risk of chronic kidney disease (CKD).

The first phase of our work was conducted between 2008 and 2012 and was presented at the 2012 Mesoamerican Nephropathy Workshop in San José, Costa Rica. This phase included the following activities:

- A **Scoping Study,** summarizing the available information on CKD in the region, identifying data gaps, and recommending research activities to address those gaps (BUSPH 2009; Ramirez-Rubio et al. 2013b; Soderland et al. 2010; Weiner et al. 2013);
- An **Investigation of CKD Prevalence and Risk Factors in Rural Nicaragua**, involving a partnership with the Brookline-Quezalguaque Sister City Committee to characterize the extent and nature of CKD in Quezalguaque, Nicaragua (O'Donnell et al. 2011);
- An **Industrial Hygiene/Occupational Health Assessment**, evaluating the potential hazards associated with chemicals and work practices at a sugarcane company in northwestern Nicaragua and providing recommendations for improving working conditions (McClean et al. 2010);
- A **Preliminary Investigation of Water Quality,** assessing approximately 200 contaminants in water samples collected from six locations selected by representatives of the affected community (Atkins et al. 2010);
- A **Qualitative Analysis of Interviews with Physicians and Pharmacists**, using data from semi-structured interviews with health professionals in Nicaragua to assess their perceptions regarding renal disease in the region (Ramirez-Rubio et al. 2013a; Ramirez-Rubio and Scammell 2011);
- A **Pilot Cohort Study**, assessing the feasibility of conducting a complete retrospective cohort study on the relationship between sugarcane work practices and CKD based on medical records in a sugarcane company (Aschengrau et al. 2012);
- An **Investigation of Biomarkers in Workers**, evaluating biological markers of kidney in-

jury and CKD in sugarcane workers in multiple jobs at pre-harvest and late-harvest, as well as miners, construction workers, and port workers (Laws et al. 2015a, b; McClean et al. 2012);

- An **Investigation of Urinary Biomarkers in Adolescents**, evaluating evidence of subclinical kidney damage among adolescents in different areas of Nicaragua, suggested by the very young age at diagnosis among many affected workers and community residents (Ramirez-Rubio et al. 2015; Ramirez-Rubio et al. 2012).

We have concluded from this work that one or more risk factors are occupational. We found that (a) sugarcane workers in northwestern Nicaragua experienced a decline in kidney function and an increase in kidney injury during the harvest, (b) measures of kidney function and kidney injury were different by job, with greatest risk observed among those in the heaviest manual labor jobs, (c) decreased kidney function was associated with longer duration of employment, (d) in the most high risk jobs, hydrating with electrolyte solution during the workday was protective against kidney injury, and (e) decreased kidney function was also observed among other heavy manual laborers such as miners, port workers, and construction workers. Our results add to the growing evidence that heat stress and dehydration play a role, possibly in combination with one or more other occupational or non-occupational factors (Brooks et al. 2012). Our work also suggests that early kidney damage may be occurring in adolescents, suggesting a possible role of genetics or early life exposures (i.e. environmental, diet, medication).

The ongoing research of the BUSPH team builds on this early work and continues to focus on occupational and non-occupational factors across the lifespan. These research efforts include collaborations with Chirag Parikh at Yale University, Sandra Peraza at the University of El Salvador, and Kate Applebaum at George Washington University. Additionally, for most of the studies described below, subject matter experts at US Centers for Disease Control and Prevention (CDC) are providing technical assistance, the CDC Foundation serves as the central administrative and coordinating lead, and an External Advisory Board has been convened to review our protocols and provide strategic direction and guidance.

Follow-up study of MeN in Quezalguaque, Nicaragua

Since 1985, the Brookline-Quezalguaque Sister City Committee (BQSCC) has had a close relationship with the municipality of Quezalguaque, located in the northwest region of Nicaragua. In the early 2000s, town health officials informed the BQSCC of a number of excess deaths due to chronic kidney disease. In 2008, the BQSCC worked in partnership with BUSPH to conduct a seroprevalence study and found an elevated prevalence of reduced eGFR, which is found disproportionately among younger males.

During the summer of 2015, we again worked in partnership with BQSCC to conduct a study in Quezalguaque designed to revisit participants from the 2008 study. Our team contacted approximately 200 of the 321 participants (or proxies) from the case-control component of the original study to determine mortality, progression, and regression among participants who had an eGFR<60, as well as new cases whose creatinine had previously been within normal limits. We collected questionnaire data and obtained blood, urine, and saliva samples. Testing for serum creatinine and other clinical measures was conducted at the ISO-certified Centro Nacional de Diagnóstico y Referencia (CNDR, a division within the Nicaragua Ministry of Health). In February 2016, we plan to attempt to enroll those 2008 participants who we did not have time to contact during summer 2015.

First, and most importantly, we aim to characterize factors associated with more rapid progression among cases, and incidence of new disease among those previously unaffected. Second, we will assess the proportion of participants who had reduced eGFR in the original study but no longer test in that range, as an estimate of the potential effect of using one creatinine measure as an outcome in epidemiological studies. Finally, we are also assessing the accuracy of a field measurement of creatinine using a point-of-care device via a comparison with laboratory-based creatinine measurements. There have been almost no studies that have characterized the effect of the CKD epidemic in communities over a period of time; this study will contribute to an understanding of the natural history of the disease and hopefully identify factors (e.g. work history, agrichemical use, hydration, etc.) that can inform future interventions to slow progression of disease and prevent new cases. The study is supported by funds from BQSCC and Santander scholarships.

Investigating genetic susceptibility to MeN

We are currently conducting multiple studies to explore the potential role of genetic susceptibility in MeN. While we believe that occupational and environmental exposures are the primary cause(s), it is possible that some exposed individuals are more prone to develop kidney disease than others. Finding genetic variants that increase risk of kidney disease may be helpful in several ways. First, the genes involved in susceptibility may tell us about the nature of the occupational/environmental factor (e.g. a liver detoxifying enzyme may point toward a toxin whereas a variant in a salt or water handling gene would implicate dehydration). Second, studies of occupational/environmental factors focusing on those individuals with an underlying genetic susceptibility may have considerably more power in some instances than studies where non-susceptible individuals are also considered. These studies include a family pedigree study and a case-control study. These complementary studies are designed to find genetic variants with a wide range of frequency, penetrance (power), and dependence on both occupational and non-occupational environmental factors. These studies are summarized below.

Family Pedigree. The family-based study is optimal for identifying strong genetic variants that are enriched in the local population. Our team has recruited approximately 300 members of 25 families with high burdens of kidney disease, including both men and women over the age of 18. These families include members of ASOCHIVIDA, a community organization of individuals with CKD, and other families known in the community to have multiple family members with CKD. We interviewed family members to construct family trees that include the relationships between family members (e.g., child, parent, spouse, brother), CKD diagnosis, and whether the person is alive or dead. Samples of urine, serum, and saliva have been collected from nearly all participants. In addition, participants responded to a questionnaire detailing occupational history (job and duration), medical problems, medications, herbal remedies, and diet.

The early phase of the project included DNA extraction from either saliva or whole blood collected from approximately 200 participants, as well as DNA quantification and rigorous quality control assays to ensure sufficient DNA quality for next-generation genetic testing. To date, whole exome sequencing has been performed for more than 50 samples. In the near future, genotype-array based linkage will also be performed. While we are still analyzing our data, one finding has been a high degree of interrelatedness between many of our independently recruited families. For example, eight of our extended families are connected by intermarriage, representing a “superfamily” with 65 individuals affected with kidney disease. Also of note are highly elevated uric acid levels in family cases. To determine whether these high levels are out of proportion to the degree of kidney dysfunction, we compared uric acid levels between cases in this cohort and similar CKD patients in the NHANES cohort. We found individuals with MeN had 2.0 mg/dL higher uric acid levels than NHANES CKD cases after correction for age, GFR, and use of uric acid lowering medications. This finding suggests that elevated uric acid metabolism could be important in the pathogenesis of MeN.

Case-Control Study. The case-control study is optimal for finding genetic variants that modify the effect of an occupational or environmental exposure. We are recruiting 360 former sugarcane workers who have been diagnosed with CKD, identified through the Institute of Social Security renal clinic, which is administered by the Ministry of Health. Controls will include 360 healthy members of the same community matched to cases by age and job description, drawn from current workers at the sugarcane company. Because 97.5% of patients at the social security clinic are men, the study will be limited to males.

Starting in 2015, we have recruited 331 active sugarcane workers as controls during the harvest season. These workers included primarily cane cutters, irrigators, pesticide applicators, and seed cutters with several years of experience in sugar cane agriculture. From each worker, we collected blood and saliva for DNA, as well as serum and urine. More than 200 cases have been recruited from the social security clinic to date. We will use whole genome genotyping arrays to identify genetic variants that differ significantly in frequency between cases and controls, followed by more detailed studies ("fine-mapping") to determine the disease-causing variant.

Preliminary data indicate that as many as 10% of subjects recruited as controls have elevated creatinine values during the zafra. In follow-up assessments of these workers with high creatinine values after the harvest, we found that most had substantial improvement in creatinine level, suggesting that AKI may be more frequent than expected. In addition, we found that CKD cases are more likely to have a brother (3-fold increase) or father (nearly 4-fold increase) with CKD than controls, supporting the idea that MeN may have a genetic component.

This family study is funded by the Doris Duke Foundation, the Satellite Healthcare Foundation, and Beth Israel Deaconess Medical Center. The case-control study has been supported by funds donated by Comité Nacional de Productores de Azúcar (CNPA), an association of sugar producers in Nicaragua, as well as funds from the Doris Duke Foundation and Beth Israel Deaconess Medical Center in Boston.

Biomarkers and risk factors for MeN among children and adolescents in Nicaragua

Building on our preliminary investigation of adolescents, we were able to locate, re-enroll, and collect new samples from greater than 80% of the students who participated in the 2011 study to assess whether kidney injury has changed during the 4 year period and whether this differs by school, or subsequent occupational factors.

We are also preparing to conduct a new cross-sectional study to determine whether children and adolescents aged 7-17 from 8 schools located in 4 different geographical areas of Nicaragua (chosen based on different population CKD mortality rates, climate, altitude, and primary industry of the region, as well as parents' occupation) show signs of kidney injury, and whether the extent of injury varies by school. We will also explore potential factors (e.g. dehydration, exposure to arsenic and other metals, nephrotoxic drugs, infections, and work history) that might lead to kidney damage. Compared to the 2011 study, the current study will be larger, cover a broader geographic area, wider age range, use a lower-risk reference group, and collect information on potential causes of early kidney damage, which was not part of the prior study. The funds for this study have been donated by CNPA, an association of sugar producers in Nicaragua.

Longitudinal investigation of MeN among Central American workers study

We have planned a large-scale longitudinal study to investigate the role of heat stress and pesticide exposure on risk of MeN among Central American workers. While the field investigation has not yet been funded, we intend to recruit a study population of 780 workers from multiple industries in Nicaragua and El Salvador. At Baseline (Round 1), we will conduct an extensive exposure characterization during three consecutive workdays. We plan to then follow this cohort of workers over time and conduct five additional rounds of sampling at six-month intervals (30 month period). In the first round, we will obtain repeated measures of exposure to heat and agrichemicals (exposure/dose), volume depletion and muscle damage (physiologic response), tubular damage (subclinical acute kidney damage), and eGFR (CKD). In later rounds (Rounds 2-6), we will primarily monitor tubular damage and eGFR to characterize the progression of change in eGFR. Monitoring workers on-site during the workday will provide the opportunity to obtain quantitative exposure measures. Additionally, revisiting workers at six-month intervals will provide the opportunity to investigate the potential for repeated subclinical acute kidney damage to progress to CKD, a process that may be uniquely observable in this population. We will evaluate occupational exposures with acute kidney injury and/or chronic kidney disease while also exploring the potential role of alcohol consumption, medication use, and dietary factors.

As part of planning for this study, we conducted a pilot study of 50 Nicaraguan sugarcane workers to obtain preliminary data on agrichemicals, metals, and arsenic (speciated and total). These 50 workers had previously participated in our study from four years earlier. At the end of the workday, we collected blood and urine samples to be analyzed for agrichemicals, heavy metals, and arsenic at the laboratories of the CDC. Serum creatinine and other clinical parameters were analyzed at CNDR, and biomarkers of kidney injury were measured at the Division of Nephrology and Hypertension at Cincinnati Children's Hospital Medical Center in the US. Analyses are on-going and we plan to present preliminary findings from this pilot study at the workshop in November, after which we can update this summary.

The first years of funding was donated by the Azucareros del Istmo Centroamericano, an association of sugar producers in Central America. We are currently pursuing the funds necessary to proceed with the field investigation, which could potentially include donations from industries, foundations, and grant funding from the National Institutes of Health.

MeN progression

The MeN progression study aims to identify modifiable risk factors that may relate to the progression of MeN, which may assist physicians and patients to slow the rate of disease progression. The study is being conducted in conjunction with the case component of the genetic case-control study. Questionnaire and biological samples are shared between the two studies. Medical records will also be abstracted and provide additional data regarding determinants of progression. Funding for this study comes from George Washington University.

Summary

The BUSPH studies represent multiple components of a single research program designed to investigate occupational and non-occupational risk factors across the lifespan. Our work to date provides evidence that one or more risk factors are occupational and we have made recommendations for improving work practices. Given that the disease likely has a multifactorial etiology, our primary goal is to identify the occupational and non-occupational cause(s) of the epidemic to inform intervention studies and minimize risk of MeN.

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Gaining insights into the evolution of CKDnt from community-based follow up studies

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Summary

Chronic Kidney Disease (CKD) is a clinical syndrome that is usually without symptoms until the condition is at an advanced stage. CKD is often identified late, and the underlying aetiology will frequently remain unknown (or recorded as due to hypertension), as renal biopsy in advanced CKD will usually reveal only interstitial fibrosis and atrophy of renal tubules (scarred kidneys). The situation is further complicated by the progressive nature of CKD, with continuing decline in kidney function even after the withdrawal or adequate treatment of an initial insult. Together these attributes mean that identification of causal factors is extremely challenging.

We have recently commenced a community-based longitudinal study examining CKDnt in Leon and Chinandega departments, Nicaragua. Although perhaps logistically more challenging, study designs of this type have the potential to provide important insights that cross-sectional survey, case-control or occupationally based cohorts cannot. In particular, community based follow-up studies are likely to provide information on the rate of progression of disease. Currently, although those with CKDnt are often told that they have abnormal kidney function, the natural history of disease is not well enough understood to inform sufferers how quickly their kidney function will decline, and whether remaining in intensive agricultural occupations will alter this trajectory. This information is clearly critical to those with CKDnt and it is only by performing representative community based longitudinal studies that the necessary data can be collected.

Funded by the UK Colt Foundation in partnership with the La Isla Foundation we recently commenced a community based follow-up study in Leon and Chinandega departments, Nicaragua. 350 participants aged 18-30 without known CKD (M:F 3:1) were recruited following local community censuses. This represents >95% of the men in these communities and a random sample of women. Study visits, which take place twice a year, have been arranged for the weeks prior to, and again in the weeks following, the zafra. Conducting a follow up study in a rural area has been, and remains, a major challenge and several issues have had to be overcome during the first year of the study. A significant obstacle has been internal and external migration. Achieving follow-up study visits in this group has required the investment of significant time and resources. Continuing community engagement has been key. A high proportion of study subject retention appears to be based on the development of good relationships with both the participants and also with the community leaders.

In summary, community based follow-up studies have several advantages over cross-sectional studies in the community or research designs based in healthcare or occupational settings. These include generalizability, reduction in selection bias, better handling of reverse causation and recall bias, along with the ability to utilize an outcome measure (within-person change in eGFR) that allows the identification of those sustaining the most significant chronic kidney injury. We hope our study along with others of similar design will provide important insights into the aetiology of CKDnt.

Introduction

Chronic Kidney Disease (CKD) is a clinical syndrome that is usually without symptoms until the condition is at an advanced stage. Even in countries with highly developed healthcare systems, in the absence of known risk factors for kidney disease such as diabetes, CKD is often identified late. In these cases the underlying aetiology will frequently remain unknown (or recorded as due to hypertension)(1), as renal biopsy in advanced CKD will usually reveal only interstitial fibrosis and atrophy of renal tubules (scarred kidneys). The situation is further complicated by the progressive nature of CKD, with continuing decline in kidney function even after the withdrawal or adequate treatment of an initial insult.(2) Together these attributes mean that identification of causal factors is extremely challenging. These problems are particularly relevant when considering the aetiology of CKD of non-traditional causes (CKDnt) where the cause(s) remain to be firmly established.

We have recently commenced a community-based longitudinal study examining CKDnt in Leon and Chinandega departments, Nicaragua. Although perhaps logistically more challenging, study designs of this type have the potential to provide important insights that cross-sectional survey, case-control or occupationally based cohorts cannot. This contribution will outline the rationale underlying our approach. It will discuss some of the theoretical advantages as well as practical challenges associated with conducting this type of investigation.

Where should we conduct our studies? Generalizability and representativeness of occupational and community cohorts

As noted above, CKD in its early stages remains asymptomatic. Therefore, unless identified on routine blood tests, those affected usually only present to healthcare services when they become unwell, i.e. with late disease. Advanced CKD also carries significant cardiovascular disease risks(3), so patients may die from stroke or cardiac causes before coming to the attention of healthcare services. As renal replacement therapy is often not a treatment option amongst affected communities, sufferers of CKDnt, in particular, may not engage with medical services at all. These issues mean that healthcare system based studies may not be optimal for identifying cases as participants may only represent a subset of those with CKDnt, i.e. those with advanced disease who choose and are able to engage with the health services. Furthermore, choosing appropriate controls is also likely to also be challenging because it may not be clear what the appropriate 'catchment population' of the health system is.

As CKDnt is thought to be, at least partly, an occupational disease(4), workplaces, specifically sugar cane production companies, are a logical place to conduct studies. This has the advantage of easier capture of both data and samples related to work-based exposures. In addition, participants recruited in the workplace are likely to be at relatively high risk of CKDnt; thus, the power to detect associations is likely to be maximized for any given sample size. However, there are several disadvantages to workplace studies that must also be considered. It is clear that CKDnt in Central America is not entirely confined to those working in sugar cane production, with women and agricultural workers growing other crops also being affected. Perhaps more importantly, however, increasing awareness of the epidemic amongst employers now means that those with impaired kidney function are either no longer employed at the beginning of the zafra or are excluded from follow-up visits in longitudinal studies encompassing the harvest period.

Community cohorts have several advantages. Firstly this type of cohort represents the entire at-risk population. Workers from all occupations and both men and women can be recruited as study participants. Assuming that the communities chosen to take part are appropriate, and generally support the study objectives, there is unlikely to be significant selection bias. Although occupational exposures may be more difficult to assess, environmental exposures in close proximity to participants' homes can be measured relatively easily. One general disadvantage of community-based studies is that they typically need to be large if disease prevalence is not high. However, given the epidemic proportions of CKDnt, this may not be such a problem when studying the disease in Central America. Finally, when considering longitudinal studies loss to follow-up, although still a significant concern, is likely to be less of challenging in community-based studies than in occupational cohorts.

Dealing with reverse-causation - longitudinal studies

Several risk factors associated with CKDnt in cross-sectional studies, although possibly reflecting a causal relationship, may also be a consequence of impaired kidney function. For example, several studies have reported an association between high volumes of fluid intake and CKDnt. This association could represent a causal effect of high levels of exposure to a water-soluble toxin, it could be a surrogate for general work intensity/heat-stress, or alternatively could be the consequence of impaired kidney function where participants with pre-existing kidney injury are unable to concentrate their urine. Other examples where it is similarly challenging to untangle causation from reverse causation and confounding include the associations of CKDnt with higher serum/urinary uric acid levels and increased alcohol intake.

Although confounding can obviously only be dealt with by appropriate measurement and adjustment, reverse causation can usually be addressed by using a longitudinal study design.

Measuring kidney function. Overcoming the issues with definition of CKD, historic exposures and between-subject variability in GFR.

Clinical CKD is usually defined on the basis of the presence of an eGFR<60mL/minute for more than 3 months(5). Although there is clinical utility in this definition, it is problematic when conducting aetiological research. As described above, CKD provides particular challenges when trying to determine the cause of disease. The initial response to any injury will not necessarily immediately manifest in a biochemical deterioration in kidney function (and in some cases such as diabetes, initially leads to hyperfiltration, an increase in eGFR; Figure 2). This means that a clearly abnormally low eGFR may not be present until a significant proportion of the kidney is scarred. Indeed, the initial source of the injury may have resolved/been removed before the eGFR falls to the level that would be used to diagnose CKD clinically.

Given this background, attempts to identify causal factors when using questionnaires, as part of a cross-sectional (usually case-control) approach, is likely to be prone to significant recall bias if an eGFR threshold of <60mL/minute is used for case definition. Furthermore, both biological and environmental samples obtained at the time of a clinical diagnosis of CKD are likely to have limited utility in these circumstances. The proposed research threshold of an eGFR of <90mL/minute, although less prone to this problem, may still occur long after the occurrence of important exposures in the natural history of the disease.

A further challenge in epidemiological CKD research surrounds the measurement of kidney function. Between-person variation in GFR is large, even amongst those without any underlying kidney disease, i.e. normal kidney function is highly variable. In addition there are considerable sources of variation when using the equations used to estimate the GFR (the eGFR) from the serum creatinine(6). Table 1 outlines some of the factors that might influence the eGFR where it is calculated from the creatinine (e.g. using the MDRD or CKD-EPI equations). Newer markers of kidney function such as cystatin-C are less prone to some of these problems.

Taken together, the above factors may mean that the absolute eGFR may not be the most useful outcome measure for research studies trying to establish the causes of nephron loss in CKDnt. For example, a low-normal eGFR in a healthy subject may be similar to another subject with impending CKDnt (Figure 2). Another possible

Figure 1. Hypothetical timing of injury and decline in eGFR.

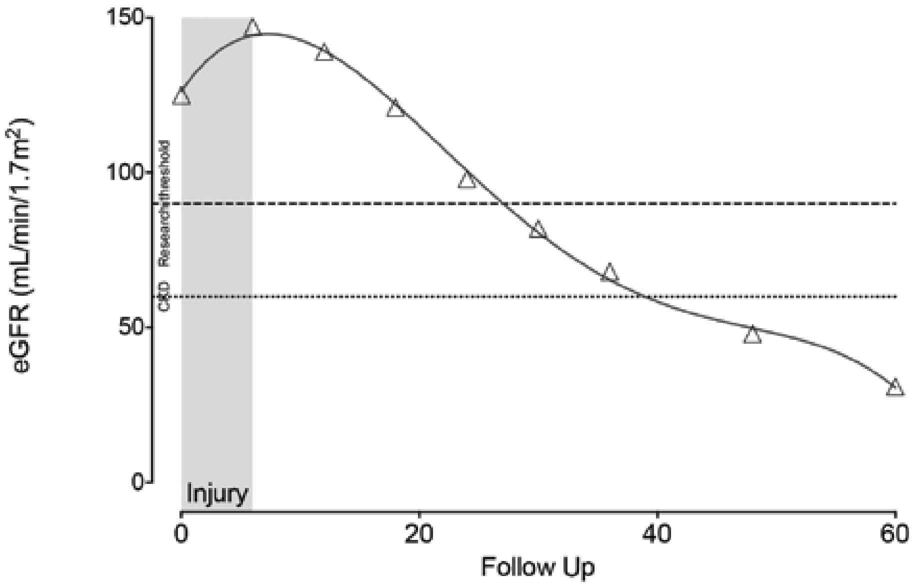


Table I. Factors influencing variation in eGFR calculated from the serum creatinine.

Between-person factors	Within-person factors unrelated to kidney clearance	Within-person factors due to changes in kidney clearance
Muscle mass (although this can also change within a person)	Animal protein meal	Functional decrease in eGFR (i.e. reduced glomerular blood flow) Due to volume depletion or vasoactive drugs.
Ethnicity	Strenuous exercise leading to muscle breakdown	Loss of nephrons (functional units of the kidney) Due to tubular or glomerular cell damage.
Sex	Drugs that alter creatinine handling (e.g. trimethoprim)	
Genetic background	Changes in plasma volume (impacts all solutes in the plasma) e.g. short term dehydration or overhydration	

outcome measures might be the development of low molecular weight (tubular) proteinuria, if a protein that accurately predicts progression to CKDnt can be identified, or alternatively within-subject change in eGFR(6). This latter outcome is advantageous in that the measure will be independent of between-person factors and if calculated across a number of time points will reduce the influence of the within-person factors that are not related to nephron loss.

Insight into the rate of progression of disease

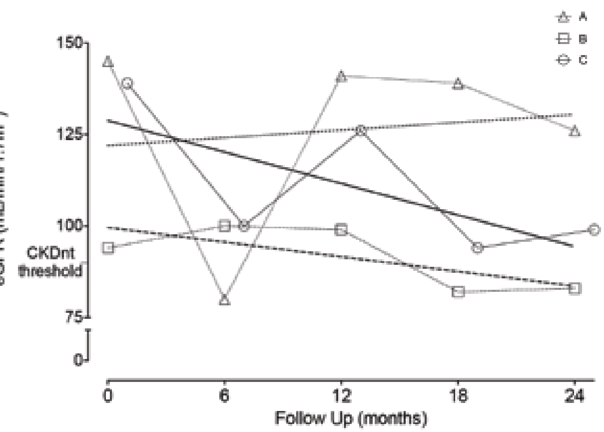
Community based follow-up studies are also likely to provide information on the rate of progression of disease. Currently, although those with CKDnt are often told that they have abnormal kidney function, the natural history of disease is not well enough understood to inform sufferers how quickly their kidney function will decline, and whether remaining in intensive agricultural occupations will alter this trajectory. This information is clearly critical to those with CKDnt and it is only by performing representative community based longitudinal studies that the necessary data can be collected.

Loss to follow-up

Loss to follow-up is one potential weakness of any longitudinal design. For cohort studies such as the one we describe here, failure to obtain follow-up eGFR measurements from each subject will substantially reduce the power of the study to detect associations. Continuous engagement with study communities including holding village meetings, ensuring that study visits are conducted at appropriate times, feedback of results of kidney tests, and exploring causes of disease felt to be important by the local community, will all be critical to the success of the study.

Subject A has normal kidney function but sustains a single acute kidney injury at 6-months which then recovers. Depending on the timing of a cross sectional study subject A could be classified as having CKDnt (using a threshold og <90mL/min). Subject B has impaired kidney

Figure 2. Theoretical example of use of within-person change in eGFR as the outcome measure in research.



function that declines slowly. Depending on the timing of a cross sectional study subject B may or may not be classified as having CKDnt. Subject C has normal kidney function which never falls below the research threshold for CKDnt during the study period however they appear to have sustained the most significant chronic kidney injury. Straight lines represent the slope of within-person change in eGFR and are more informative than absolute values.

Early experience of conducting a community follow-up study in Leon and Chinandega departments, Nicaragua

Funded by the UK Colt Foundation in partnership with the La Isla Foundation we recently commenced a community based follow-up study in Leon and Chinandega departments, Nicaragua. 350 participants aged 18-30 without known CKD (M:F 3:1) were recruited following local community censuses. This represents >95% of the men in these communities and a random sample of women. Study visits, which take place twice a year, have been arranged for the weeks prior to, and again in the weeks following, the zafra. Detailed questionnaires were conducted by trained interviewers and baseline clinical data, biological and environmental samples collected. A total of five study visits are planned. The second visit took place in May/June 2015 and the third visit is planned for October 2015. Participants receive their kidney test results within a fortnight of the study visits. Additionally participants receive reimbursement of expenses and any lost income they have incurred to attend the study visit. Approximately 90% of the initial cohort attended for the second study visit.

Conducting a follow up study in a rural area has been, and remains, a major challenge and several issues have had to be overcome during the first year of the study. A significant obstacle has been internal and external migration. At the end of the harvest around 30% of the study population had left their communities, to go to Costa Rica or other departments in Nicaragua, to look for alternative employment during the non-harvest period. Achieving follow-up study visits in this group has required the investment of significant time and resources.

Secondly, the small number of participants who were working during the pre-harvest has been an issue. As the workday starts very early in the morning and finishes late in the afternoon it has been difficult to identify suitable times to conduct the data collection.

Finally, the real or perceived fear of job loss is ever present. Participants have reported that employers have told them that they will not be allowed to work if they participate in research projects. Although study visits have been timetabled to occur outside of the zafra, employees still express the concern they will be sacked and permanently lose their livelihoods.

Continuing community engagement has been key. A high proportion of study subject retention appears to be based on the development of good relationships with both the participants and also with the community leaders.

Conclusions

Community based follow-up studies have several advantages over cross-sectional studies in the community or research designs based in healthcare or occupational settings. These include generalizability, reduction in selection bias, better handling of reverse causation and recall bias, along with the ability to utilize an outcome measure (within-person change in eGFR) that allows the identification of those sustaining the most significant chronic kidney injury. We hope our study along with others of similar design will provide important insights into the aetiology of CKDnt.

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What is known about the burden and clinical characteristics of Mesoamerican nephropathy?

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The prevalence and burden imposed by Chronic Kidney Diseases (CKD) in Central America is mostly unknown as no national or regional registries are in place and no national prevalence studies are available. While CKD causes are diverse and some associated with known chronic non-communicable diseases (diabetes mellitus, hypertension) as happens elsewhere, the emergence of a major CKD epidemic known as Mesoamerican Nephropathy (MeN) or CKD of unknown origin (CKDu), has drawn the attention of health authorities and international organizations that have made efforts to understand the magnitude of this public health problem. Here we review the situation in four Central American countries (El Salvador, Nicaragua, Guatemala, and Costa Rica) where some data are available. Then we present an overview of what we know currently about Mesoamerican Nephropathy in this region.

Current data for a review of each country's MeN experience are obtained from scarce published articles, hospital records, and verbal communications and only allow crude and fragmented estimates of the burden of this disease. Table 1 summarizes the status of MeN in the region and is described in detail below.

Burden of disease in Central America:

El Salvador

There are four reports on the prevalence of MeN in different parts of El Salvador, ranging from 10 to 18%, with prevalence predominating in males.

In 2005, García--Trabanino and coworkers reported a cross-sectional study that explored the prevalence of CKD among males in eleven communities at different geographic altitude (meters above sea level = masl); eight villages were located at the coast (n=291) and three at an altitude above 500 masl (n=62). This investigation included two phases; in the first interviews were performed and tests for albuminuria (dipstick +) performed in all 253 persons. The study found proteinuria in 46% of the coastal area subjects vs 13% at higher altitude. Those positive for albuminuria at the coast were included in the second phase where samples for serum creatinine (SCr) were collected successfully from 80 of 133 with albuminuria. CKD (SCr >1.5 mg/Dl) occurred in 37 cases (13%) with only 14 (38%) with a history of diabetes or hypertension. The remaining (62%) did not appear to have a clear-cut cause for CKD. (1)

In 2009, Orantes and coworkers, conducted a study in the Bajo Lempa Region in search of MeN cases. They recruited a total of 375 families and 775 individuals (343 men, 432 women, average age 39) were studied (88% of the total resident population in the region). Elevated prevalence of risk factors was observed: diabetes mellitus, 10%; hypertension, 17%; family history of chronic kidney disease, 22%; dyslipidemias, 63%; overweight, 34%; obesity, 22% (twice as common in women); metabolic syndrome, 29%; use of non-steroidal anti-inflammatory drugs, 75%; infectious diseases, 87%; agricultural occupation, 41% (81% in men); and contact with agrochemicals, 50% (83% in men). Prevalence of renal damage markers was 16% (greater in men): microalbuminuria 6%; proteinuria 6%; hematuria 4%; proteinuria–hematuria 0.3%. Proteinuria of <1 g/L predominated. Prevalence of chronic kidney disease (persistent abnormality during 3 months) was 18% (26% in men; 12% in women).

Distribution by stages: stage 1, 5%; stage 2, 4%; stage 3, 6%; stage 4, 3%; stage 5, 0.6%. Of the cases of CKD stage 1-5 86% did not have diabetes mellitus, and 55% of the CKD cases were associated with neither diabetes nor hypertension. Prevalence of chronic renal failure (CKD stage 3+) was 10% (17% in men; 4% in women). (2)

In 2012, Peraza and coworkers performed a study of 256 men and 408 women from 5 communities. They defined CKD as eGFR <60 ml/min/1.73m2. Two communities, one rural and the other semi-rural, were located at the coast at less than 500 masl communities was sugarcane agriculture. Differences in CKD by sex were similar in the two communities: in the rural community, 19% men and 8% of women and in the semi-rural community 18% and 8%, respectively. In a third community located at more than 500 masl, sugarcane agriculture predominated but only 2% of the men and 3% of the women had CKD. A fourth community of coffee growers located at 1650 masl had CKD in no men and only 1% of women. The fifth community was urban and located at 650 masl. In this community no men and just 2% of the women had eGFR below 60 ml/min/1.73m2 CKD, although 9% of men and 11% women had abnormal SCr, probably not related to MeN. The high prevalence of eGFR <60 mL/min/1.73 m2 in the coastal communities - 19% of men aged 20-60 years, indicates the severity of the epidemic in region where there is little to offer to patients and where CKD often progresses to ESRD and death.(3)

The last study published in 2014 by Orantes et al was performed in 3 communities: Bajo Lempa, Guayapa Abajo, and Las Brisas. The prevalence of all stages of CKD was 18% among 2388 adults, men and women. The prevalence of CKD with neither diabetes nor hypertension nor proteinuria ≥1 g/L (51.9%) was 11% (17% in men and 7% in women). Prevalence of renal damage markers was 13% (higher in men): microalbuminuria 7%;proteinuria (≥0.3 g/L) 2%; and hematuria, 1.5%. CKD was significantly associated with male sex, older age, hypertension, agricultural occupation, and family history of chronic kidney disease. (4)

Nicaragua

While there are some reports from this country the burden of the disease is unknown. In 2010 a cross-sectional study of 1096 subjects from 5 communities, four at sea level and 1 at high altitude, was performed. CKD was defined as eGFR of <60ml/min/1.73 m^2. The first community included individuals working in mining and subsistence farming; low eGFR was observed in 19% of men and 5% of women. A community of workers from banana and sugar cane plantations displayed the highest CKD prevalence: 22% in men and 6% in women. A fishing community had a CKD prevalence of 13% men and 4% women. A fourth community with service workers (street vendors for example) had no CKD cases, and in the fifth coffee community, at high altitude, 8% of men and no women had low eGFR. (5)

In the rural municipality of Quezalguaque, 771 members from 300 randomly selected households were studied: 13% had eGFR of <60 ml/min/1.73m^2. Of those with reduced eGFR, 89% lived in the lowlands (<500 masl) with a mean age of 55; 61% were male. Among young people between 18 and 30 years, 3% of the 278 participants had eGFR <60 ml/min/1.73m^2. (6)

Another study near the town of Chichigalpa recruited 424 individuals of whom 151 were agricultural workers. The prevalence of low eGFR was 42% in men and 10% in women and microalbuminuria was present in <10%. CKD was not associated with diabetes, NSAIDs or hypertension. Among risk factors identified for CKD development were amount of sugarcane cutting (OR 5.9), inhalation of pesticides (OR 3.3), and chewing sugar cane (OR 3.2). (7)

A recent cross sectional study among 2275 individuals aged 18-70 in the Municipality of León (64% urban population) showed that the overall prevalence of eGFR <60ml/min/1.73m^2 was

9%, 14% men and 6% women. Rural areas had a higher prevalence than urban areas, 13% vs 7%. Significant CKD risk factors were: increasing age; living and working in rural areas, low education, and increasing years of agriculture work. (8)

Costa Rica

A study published in 2005 reports a national prevalence of 193 ESRD patients/million inhabitants. The main causes were diabetic nephropathy and hypertension, but a different pattern of ESRD appeared in the Guanacaste province where the number of new cases has reached epidemic proportions, all affected being young men working as sugar cane cutters and between the ages of 20 and 40 years. The clinical picture was concordant with what is usually seen in chronic tubular interstitial nephritis and a few biopsied cases confirmed this histopathological pattern. (9)

During 1970-2012, age-adjusted CKD related mortality increased in the province of Guanacaste, among men from 4.4 to 38.5/100 000 vs 3.6 to 8.4 in the rest of Costa Rica, and among women from 2.3 to 10.7/100 000 vs 2.6 to 5.0 in the rest of Costa Rica. During the period 2008-2012, the mortality rate among males was almost 9 times higher than in the rest of Costa Rica but also among females twice as high as compared to the rest of the country. (10)

Guatemala

There are only scarce data about the prevalence of CKD or end-stage renal disease (ESRD) or CKD mortality in this country. Guatemala presented data on CKD in a 2013 meeting sponsored by COMISCA/PAHO. PAHO reported CKD and end stage renal disease (ESRD) incidence of 1069 new cases in 2009 and 1422 in 2012. Prevalence of CKD/ESRD in the year 2012 was highest in the capital city (1468 cases), followed by the Escuintla (231 cases), Santa Rosa (173) and Jutiapa (154) departments, all located on the Southwest Pacific coast of Guatemala. At the COMISCA/PAHO meeting CKD associated mortality rates in 2007 were reported as 6/100,000 inhabitants with a male/female ratio of 7/6, and increased to 9.6/100000 for 2010. In 2008, the highest mortality occurred along the Pacific coast, in particular in the Department of Retalhuleu with 30.9/100,000 inhabitants, followed by Santa Rosa with 20.36/100,000 inhabitants.(11)

Recently an investigation was conducted of 3,105 patients with ESRD in renal replacement therapy (RRT). Dialysis enrollment was positively correlated with the Human Development Index and with literacy rates overall suggesting better access to dialysis services in higher socioeconomic regions. But the same data showed that dialysis rates were highest in the poor southwest coastal region where both peritoneal dialysis and hemodialysis were more common in men than women – significantly different for those on peritoneal dialysis (58% male). This geographic area is where sugar cane plantations are located and where higher daytime temperatures are recorded. The etiology of cases of ESRD is not described in this study but many cases could be MeN as the geographic distribution of dialysis cases resembles the situation in Nicaragua and El Salvador: i.e. higher in the high temperature and sugar cane growing regions. Therefore, it is likely that the epidemic of CKDu extends throughout the Mesoamerican region. (12)

Mortality due to CKD chronic kidney disease and renal failure in Central America

PAHO reports that in the past two decades, a disconcerting increase in CKD has been observed in Central America, causing thousands of deaths. According to the available data, the mortality rates >10 deaths/100,000 from chronic kidney failure (ICD 10, N-18) in the Americas are, in descending order, Nicaragua (42.8), El Salvador (41.9), Peru (19.1), Guatemala (13.6), and Panama.(12.3) Canada and Cuba have reported the lowest mortality rates in the Region. Mortality in Nicaragua and El Salvador was 17 times higher compared to Cuba, and in these countries three times higher for men than for women, but rates among women were also higher than in other countries. (13)

Clinical and laboratory characteristics:

The development of MeN in agricultural workers is accompanied by non-specific clinical manifestations. Some of the most frequent symptoms reported by workers are related with heat stress and physical effort: muscle spasms, cramps, arthralgia, dysuria, nausea, vomiting, headache, asthenia, profuse sweating, and shortness of breath, distal edema and lumbar pain; yet these symptoms are not direct manifestations of MeN (14,15). Often affected individuals employ NSAIDS, antibiotics, diuretics or herbal medicines by self-prescription, or prescribed by general practitioners or non-physicians, which may add to the renal injury (15). At later stages of CKD the clinical scenario is identical to that seen in most other causes of advanced uremia or ESRD.

Patients are usually normotensive (1,3,16) or slightly hypertensive (2,4,5,17) and most relevant biochemical findings are: hypokalemia and hyponatremia (16,17,18), hypermagnesuria andhypophosphaturia (17), and hyperuricemia(19, 20). Patients do not present significant proteinuria but microalbuminuria has been reported (1,2,3,16,17,18). Some studies have reported increased biomarkers of tubular injury: NAG, IL-18 (16,17,18) and β2 microglobulin (16,17,18,21).

A common pattern of behavior is usually slow yet progressive decline of renal function. Imaging studies are scarce yet some have revealed ultrasound images with loss of cortico-medulary relation and small kidneys (22). Early pathology studies demonstrate chronic glomerular damage with widespread glomerulosclerosis and mild to moderate chronic tubulointerstitial changes. (16,18,23)

Risk factors

Identified risk factors are: strenuous physical work and warm weather in coastal areas less than 500 masl with repeated daily dehydration, agricultural work, in particular sugarcane, and other crops like banana (5,22) and subsistence farming (5,16,23). Other identified factors are: male gender; increasing age, low socio-economic status; use of NSAIDs and herbal medicines and exposure to agrochemicals.(24)

Diagnosis and treatment of MeN

As discussed, MeN is a tubulointerstitial nephropathy that in most instances evolves to ESRD without abundant specific symptoms. This behavior is similar to most other tubulointerstitial nephropathies, therefore there is a strong need to have a high suspicion level in individuals exposed to risk factors. It is mandatory to perform periodic clinical and biochemical evaluations for those at risk to identify, as early as possible, a disease pattern that suggests the presence of MeN (16,18,22,23,24)

Prevention is the best possible action, yet there is a lack of precise knowledge of causal specific factors. We strongly believe that improvement in working conditions, including less continuous sun exposure, shaded areas for rest, and optimal rehydration would reduce the magnitude of this epidemic. While pesticides have not been proven as causal of CKD, there is no doubt that they are harmful to health; we strongly encourage elimination of those banned in other environments given their toxicity and proper protection for those exposed to agrochemicals. Education in relation to avoidance of excessive alcohol, NSAIDS abuse and herbal medicine exposure is also relevant. Finally, it is of upmost importance to view this in a holistic way. Improvement of sanitary, economic, and educational conditions will lead to a better environment to reduce the risk of development of MeN and other diseases.

Once the disease is present, treatment is not different to what is offered to other patients with tubulointerstitial diseases, including correction of hyperuricemia and/or hypertension if present. Dietary measures need to be individualized yet once the disease has progressed to Stages 3-4, there will be a need to reduce protein intake and possibly potassium and sodium. Avoidance of exposure to nephrotoxic agents is of upmost importance. When the patient develops ESRD, RRT is required with hemodialysis, peritoneal dialysis, and ideally transplantation. Unfortunately in most of the countries, the availability of proper follow up of RRT is profoundly limited as discussed above.

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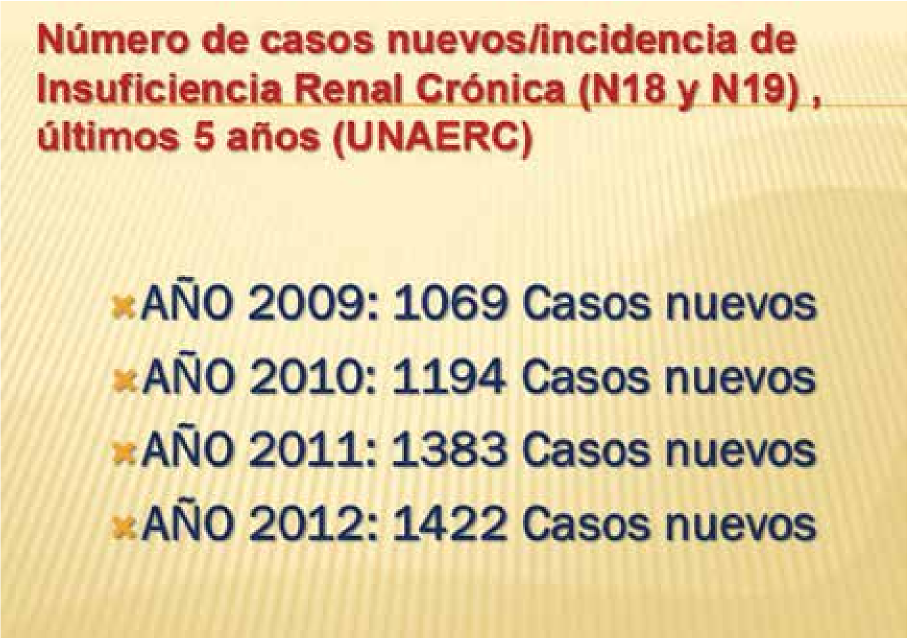
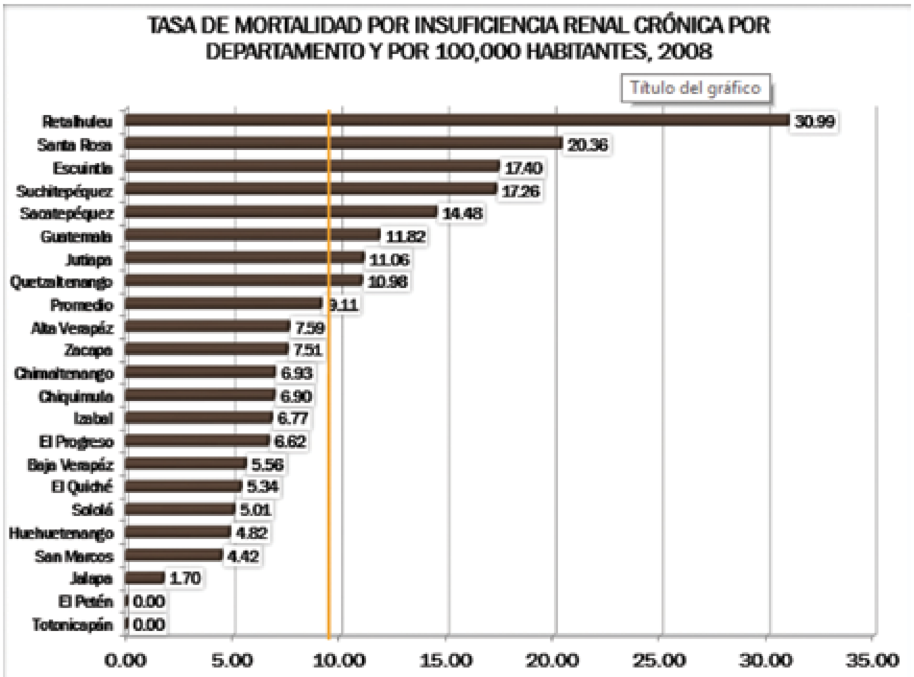
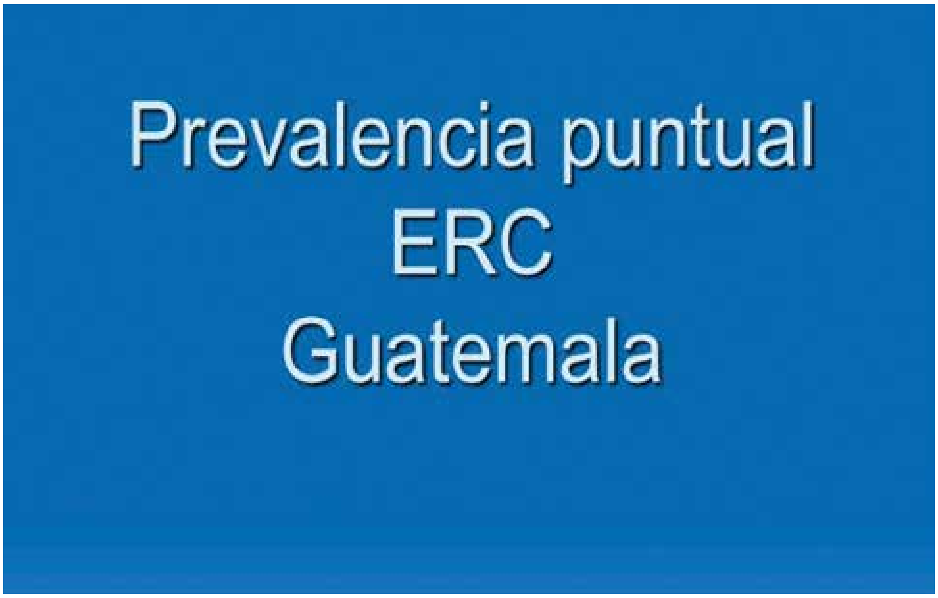
Appendix

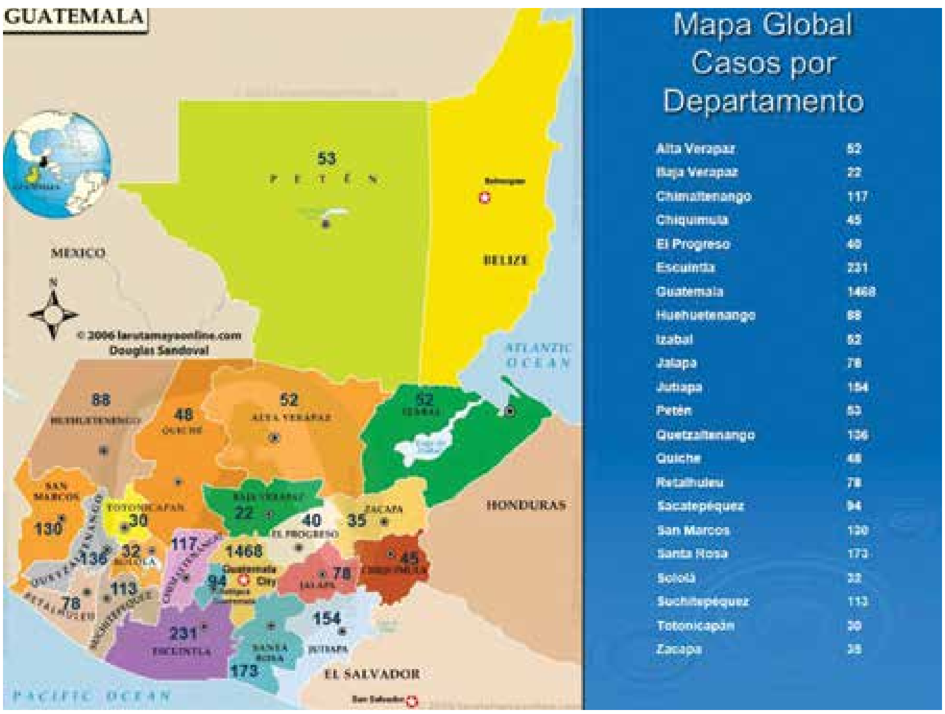
Data for Guatemala CKD/ERDS. COMISCA/PAHO meeting, San Salvador, El Salvador. April 20, 2013.




Tasa de mortalidad de ERC x 100 000 hab (por año, sexo, edad) Códigos CIE 10: N18 y N19
Instituto Nacional de Estadística
Año 2007: 6 X 100,000 habitantes.
Hombres: 7 X 100,000 Hombres.
Mujeres : 5 X 100,000 Mujeres.
Año 2010: 9.6 X 100,000 habitantes.
Mortalidad por edad. Año 2012
17 años 10% del total x ERC
18 – 59 años 39% del total x ERC
60 años a mas 49% del total x ERC


TASA DE MORTALIDAD POR INSUFICIENCIA RENAL CRÓNICA POR DEPARTAMENTO Y POR 100,000 HABITANTES, 2008
Título del gráfico
Retalhuleu 30.99
Santa Rosa 20.36
Escuintla 17.40
Suchitepéquez 17.26
Sacatepéquez 14.48
Guatemala 11.82
Jutiapa 11.06
Quetzaltenango 10.98
Promedio 9.11
Alta Verapáz 7.59
Zacapa 7.51
Chimaltenango 6.93
Chiquimula 6.90
Izabal 6.77
El Progreso 6.62
Baja Verapáz 5.56
El Quiché 5.34
Sololá 5.01
Huehuetenango 4.82
San Marcos 4.42
Jalapa 1.70
El Petén 0.00
Totonicapán 0.00
0.00
5.00
10.00
15.00
20.00
25.00
30.00
35.00


Prevalencia puntual
ERC
Guatemala


GUATEMALA
MEXICO
BELIZE
HONDURAS
EL SALVADOR
PACIFIC OCEAN
ATLANTIC OCEAN
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Douglas Sandoval
Mapa Global
Casos por
Departamento
Alta Verapaz 52
Baja Verapaz 22
Chimaltenango 117
Chiquimula 45
El Progreso 40
Escuintla 231
Guatemala 1468
Huehuetenango 88
Izabal 52
Jalapa 78
Jutiapa 154
Petén 53
Quetzaltenango 136
Quiche 48
Retalhuleu 78
Sacatepéquez 94
San Marcos 130
Santa Rosa 173
Sololá 32
Suchitepéquez 113
Totonicapán 30
Zacapa 35

Pathology and pathophysiology of Mesoamerican nephropathy and comparisons with hypertension/diabetes CKD and CKD of unknown cause outside Mesoamerica

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Background

Kidney biopsies are an important and often routinely performed procedure in the clinical investigation of patients with newly diagnosed chronic kidney disease (CKD). The morphology in the kidney biopsies usually reveals the underlying renal disease, i.e. the diagnosis. It also provides the nephrologist with information regarding the severity of the disease, the degree of chronic vs active disease and subsequently how the disease should be treated and the prognosis.

In many Central American countries kidney biopsies are not routinely done due to shortage of health care resources and/or of renal pathologists. Consequently, only a few biopsies from patients with Mesoamerican Nephropathy (MeN) are available and only two studies on the morphology have been published. In Sri Lanka, a few published studies have described the renal morphology of the chronic kidney disease of unknown cause (CKDu) affecting rural inhabitants, but a direct comparison with the biopsy studies done in Central America is difficult due to different inclusion criteria.

We here present an overview of findings in biopsy studies from three endemic kidney diseases: MeN in Central America, CKDu in Sri Lanka and aristolochic acid nephropathy (Balkan nephropathy or Chinese herb nephropathy). For comparison, we also display the typical biopsy findings in diabetic nephropathy and hypertensive nephrosclerosis, being the two most common causes of end stage renal disease in the US, Europe and Latin America.

Morphology in Mesoamerican nephropathy (Figure 1A)

In 2013 our group published the first study on the renal morphology in patients with MeN (1). Kidney biopsies from eight male agricultural workers with suspected MeN in El Salvador were analyzed. The included patients had an eGFR 27-79 (mean 46) ml/min/1.73m^2 and the morphology was similar in all eight patients. The changes seen were chronic glomerular damage with widespread glomerulosclerosis (29-78%), hypertrophy of the remaining glomeruli, signs of glomerular ischemia with wrinkling of glomerular capillaries or thickening of Bowman's capsule and mild to moderate chronic tubulointerstitial changes (tubular atrophy, interstitial fibrosis and interstitial inflammation). Vascular changes were only mild. Immune complex disease was excluded by immunofluorescence. By electron microscopy podocytic changes were shown. Our group suggested from findings that the widespread glomerulosclerosis was not only secondary to the tubulointerstitial changes seen and that mechanisms that could cause primary glomerular damage should be further investigated. A similar study has recently been performed in Nicaragua (manuscript in preparation).

López-Marín et al published in 2014 a study of renal biopsies from 46 participants (36 males and 10 females) in El Salvador with chronic kidney disease of unknown cause (2). eGFR of the included participants ranged between 30-89 ml/min/1.73m^2. They reported that 59% of the participants (67% of the males) had global glomerulosclerosis in ≥25% of included glomeruli and 40% of the participants displayed glomerular hypertrophy. Severe interstitial fibrosis was reported in 26% (33% of males) of the cases and tubular atrophy was ≤25% in 87%

of the participants. López-Marín et al conclude their findings show chronic tubulointerstitial nephropathy with secondary glomerular and vascular damage. Immunofluorescence studies were negative, but electron microscopy was not performed.

These two biopsy studies report similar findings with regards to the glomerular and tubular changes but the study by López-Marín et al reports a higher prevalence of severe interstitial fibrosis. The somewhat different findings in these two studies may be due to difference in the selection of participants or difference in the evaluation by the pathologists.

Sri Lanka

Around year 2000, an increasing number of CKD without traditional risk factors was reported from the North Central Province in Sri Lanka. In 2011, Athuraliya et al (3) presented a prevalence study of CKD in three rural communities in the North Central, Central and Southern Provinces. They showed that in one community, Medawachchiya in the north, dry region, 87% of CKD cases did not have a clear cause or risk factor. Of these participants 26 underwent kidney biopsy with morphological findings reported as tubulointerstitial disease. A more detailed description of the renal morphology was provided by Nanayakkara et al (4) who examined 64 renal biopsies and concluded that the findings by light microscopy represented a tubulointerstitial disease with interstitial fibrosis and tubular atrophy. However, they also reported a high percentage of global glomerular sclerosis (37%), glomerular enlargement (37%) and wrinkling of the glomerular capillaries, e.g. findings that also have been reported from kidney biopsies in MeN-patients. In both studies from Sri Lanka immunofluorescence studies were negative but electron microscopy was not performed.

In most studies from Sri Lanka proteinuria or albuminuria have been used for screening of CKD and inclusion in the studies. This contrasts to the studies of MeN patients who have been screened by serum creatinine and often lack or only have low grade of proteinuria. The difference in inclusion criteria makes it hard to do comparisons between the findings in the biopsy studies performed hitherto.

Aristolochic acid nephropathy (Balkan nephropathy or Chinese herb nephropathy)

A high incidence of CKD was described in certain villages on the Balkan peninsula in the 1950’s and later a close association with upper urinary tract carcinomas became evident (5). The endemic was named Balkan Endemic Nephropathy (BEN) and the renal morphology displays extensive interstitial fibrosis and tubular atrophy while glomeruli are relatively spared (6). However, some secondary vascular and glomerular lesions may be present (7). For many years the etiology behind the disease was unknown. In 1993 a report from Belgium was published describing nine women developing interstitial fibrosis and renal failure after intake of slimming herbs containing aristolochic acid (8). The renal morphology was found to be similar with BEN cases and the Belgian patients also developed urothelial carcinoma (7). Aristolochic acid had been proposed as a possible etiology in BEN in the 1970’s, because an aristolochic acid containing plant was found growing in wheat fields in endemic areas and might have contaminated the flour. But this hypothesis was for many years forgotten until the report from Belgium. Further studies have identified aristolactam-DNA adducts and specific TP53 mutations in renal tissue of patients with BEN (9) and also in patients with urothelial malignancies, associated with the use of herbal medicines containing aristolochic acid in Taiwan. Thus, the diseases are regarded to have the same etiology.

Hypertensive nephrosclerosis (Figure 1B)

Kidney damage due to hypertension can by divided into “benign/chronic” nephrosclerosis and “malignant” nephrosclerosis. In malignant hypertensive nephrosclerosis the patient presents with very high blood pressure and in the kidneys petechial hemorrhage can be found on the subcapsular surface and sometimes areas of infarct are seen. A typical lesion for malignant hypertension is thrombotic microangiopathy (thrombosis in arterioles), arteriolar fibrinoid necrosis and arteries with intimal fibrosis (10). In "benign" or chronic nephrosclerosis the typical lesions are thickening of the tunica media (i.e. the smooth muscle layer) in the vascular wall, intimal fibrosis and hyalinization of afferent arterioles. The vascular changes cause a narrowing of the afferent arterioli and a subsequent increase in vascular resistance (11). The vascular lesions result in ischemic changes of the glomeruli with glomerulosclerosis and/or wrinkling of the glomerular basement membrane. Focal segmental sclerosis may be present in some cases. Tubular atrophy and interstitial fibrosis is also present. By electron microscopy podocyte foot process effacement and widening of lamina rara interna in the glomerular basement membrane may be seen. Immunofluorescence studies are negative.

The diagnosis of hypertensive nephrosclerosis is made when a combination of these lesions is present and no other lesions indicating primary glomerular disease are found.

Diabetic nephropathy (Figure 1C)

Diabetic nephropathy is the most common cause of chronic kidney disease worldwide (12, 13). The morphological picture, first described by Gellman et al 1959 (14), is similar in type I and type II diabetes and may include changes in the glomerular, vascular and tubulointerstitial compartments. The earliest lesion is thickening of the glomerular basement membrane which only can be detected by electron microscopy. Later, there is a mesangial expansion in the glomerulus which is found by light microscopy. The mesangial expansion, caused by an increase in mesangial matrix and or mesangial cells, could be diffuse or nodular (so called Kimmelstiel Wilson lesions) and finally results in global glomerulosclerosis. Typically, the glomerular changes are accompanied by hyalinosis in the efferent arterioli. The latter lesion can be used to distinguish between diabetic and hypertensive nephropathy. In the arteries, nonspecific arteriosclerosis is often seen with intimal fibrosis and sometimes hyperplasia of the tunica media. The tubulointerstitial changes, which are not specific for diabetic nephropathy, include tubular atrophy and interstitial fibrosis, often with an inflammatory component. Immunofluorescence for immunoglobulins, comple-

Table 1: Morphological features by nephropathy

	Glomerular ischemia	Glomerular sclerosis	Chronic vascular changes	Tubular atrophy	Interstitial fibrosis	Inflammation
MeN	++	++	-	+	+	+
CKDu in Sri Lanka	?	+(+?)	+	+	+	+
Aristolochic acid nephropathy	+	- (+ late)	- (+ late)	++	++	+
Hypertensive nephrosclerosis	++	++	++	+	+	+
Diabetic nephropathy	-	+	++	+	+	+

ment and light chains should be performed to rule out other causes of renal disease. An international consensus classification system for the progressive glomerular changes with a separate scoring of the vascular and tubulointerstitial lesions was published 2010 (15). At present, renal biopsy in diabetes is only indicated when there is suspicion of another glomerular disease than diabetic nephropathy. However, several authors suggest that the indications for renal biopsies should be broadened in order to rule out treatable non diabetic renal disease (16, 17). The pathogenesis of diabetic nephropathy is not understood. It has been considered as a microvascular disease, but lately an important role of the podocyte has been suggested involving loss of cells and alterations in signaling pathways. In a recent review by Reidy et al, interrelated changes in podocytes, mesangial- and endothelial cells are suggested (18).

Conclusion

We here demonstrate the morphology of three endemic chronic kidney diseases from Central America, Sri Lanka and the Balkans and also the morphology in the two most common causes of CKD with changes in the glomeruli; hypertensive nephrosclerosis and diabetic nephropathy. These diseases share some morphologic characteristics, but they also have specific features (Table 1). In diabetic nephropathy, nodular glomerulosclerosis is typical and not seen in the other diseases. Aristolochic acid nephropathy is characterized by extensive interstitial fibrosis often with spared glomeruli. Signs of glomerular ischemia with wrinkling of the glomerular basement membrane are seen in hypertensive nephrosclerosis but also in the Sri Lankan and Central American CKD epidemics. However, in hypertensive nephrosclerosis significant vascular changes are seen, but in MeN and CKDu in Sri Lanka, most cases show minor vascular changes.

Since some of the morphological features seen in diabetic nephropathy and hypertensive nephrosclerosis also are found in the CKD epidemic in Central America, we believe it is important to exclude diabetes or uncontrolled hypertension when performing biopsy studies of patients with CKD of unknown cause in other parts of the world.

A key question that still remains unanswered is if MeN and CKDu in Sri Lanka have the same renal morphology and subsequently a possible joint etiology. As of today, the reported findings in renal biopsies from Central America and Sri Lanka cannot answer this question. To investigate the renal morphology in possible cases of MeN/CKDu in Sri Lanka, patients with diabetes and uncontrolled hypertension should be excluded. Finally, we want to emphasize the importance of performing a thorough evaluation of the biopsies by combining light microscopy, immunofluorescence and electron microscopy.

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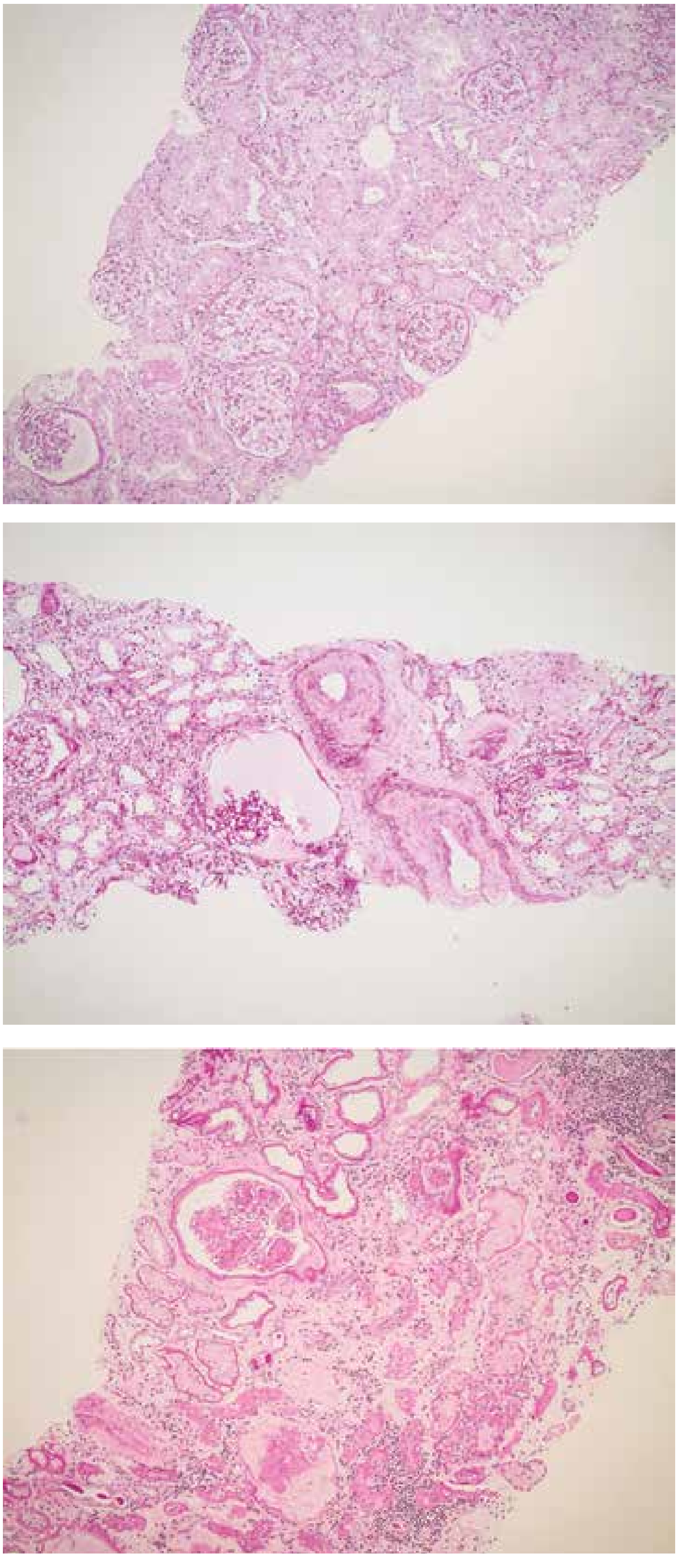
Figure legend:
Figure 1, A-C:
A: Light microscopy, MeN (Periodic Acid Schiff staining, PAS): Global glomerulosclerosis is seen (white arrow). Non-sclerosed glomeruli show signs of chronic ischemia with thickening of Bowman's capsule and wrinkling of capillaries (black star), despite normal arteries (long black arrow).
B: Light microscopy, Benign nephrosclerosis (PAS): In addition to global glomerulosclerosis (white arrow), severe intimal fibrosis is seen in an artery (long black arrow). Non-sclerosed glomeruli show signs of chronic ischemia with collapse of the glomerular tuft and wrinkling of capillaries (black star).
C: Light microscopy, Diabetic nephropathy (PAS): The typical nodular glomerulosclerosis (black star) is seen in addition to global glomerulosclerosis (white arrow). An arteriolus show hyalinosis (long black arrow).
A-C: Varying degrees of tubular atrophy (short black arrow) and interstitial fibrosis (blue star) is seen in all biopsies.



Exploring biomarkers for early evidence of abnormal kidney function

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Desired output: The best possible consensus of which biomarkers to use for early detection of abnormal kidney function. Priority of single, or combinations of biomarkers to serve as study endpoints in field and laboratory studies on Mesoamerican nephropathy (MeN) or Chronic kidney disease (CKD) of non-traditional causes (CKDu).

Report: A biomarker is an analyte in a biologic fluid that that can be used as a marker of disease, presence of an exposure, or to predict outcome/prognosis. Examples of biomarkers of disease are plasma/serum creatinine which can be used to diagnose CKD, biomarkers that can be used to identify and assess or diagnose exposure to a chemical/pollutant or infectious agent (e.g. using an antibody test) and those that can predict outcome, or serve as risk factors for disease, such as proteinuria. However, biomarkers do not need to have a physiological role.
The use of biomarkers in clinical care, surveillance/prevalence and research studies is vast. Sensitivity and specificity to correctly diagnose disease or abnormality are key features when assessing the usefulness of a biomarker´s diagnostic potential.

For assessing renal function, the use of creatinine measurements in plasma (or serum) to estimate the glomerular filtration rate (eGFR) is currently the standard. However it is necessary to use IDMS calibrated methods for creatinine determinations to get comparable and reasonably accurate results. Cystatin C is another useful marker of eGFR, in particular when the muscles mass of examined individuals is abnormal or subject to change, as this may bias the eGFR from creatinine. To analyse both creatinine and cystatin C in plasma, and to use a combined equation for eGFR increases precision (1) (2), but also the cost.

The urine albumin to creatinine ratio (ACR) is another, independent and very useful biomarker for detecting presence of CKD and estimating prognosis. When using spot or morning urine samples, adjustment for dilution using the creatinine concentration in urine is recommended.

In research studies on MeN/CKDnT the use of a number of other biomarkers in urine may be helpful and informative. What one chooses depends on the hypothesis to be tested. Following serve as examples.

- For early detection of tubular injury:
  - neutrophil gelatinase-associated lipocalin (NGAL)
  - protein HC
  - beta-2 microglobulin
- for inflammation

    - » C-reactive protein (CRP)
    - » IL-6m
- · for oxidative stress
    - » superoxide dismutase (SOD)
    - » reduced glutathione (GSH)
    - » oxidized low density lipoprotein (ox-LDL)
- ▪ for fibrosis
    - » angiopoietin 1 and 2.

A few of these urinary biomarkers have been used, but not validated, in the context of Mesoamerican Nephropathy.

Finding biomarkers for recurrent subclinical acute kidney injury and progression to CKD would be of great value. Unfortunately, the available biomarkers, other than ACR and those used to estimate GFR, have not yet been shown to predict the development or progression of CKD.

Working group recommendations regarding biomarkers for diagnosing and surveillance of MeN/CKDnT

- Measure plasma/serum creatinine using a validated method for estimating GFR.
- Analyze urine for albumin to creatinine ratio (ACR) to help assess type/cause of CKD
- Measure cystatin C combined with creatinine for more accurate eGFR in research setting if resources allow.
- As yet, no other well-validated biomarkers for early detection and prognosis of CKD are available. Future research to identify such biomarkers is encouraged, but will require longitudinal studies.

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Exploring genetic and epigenetic susceptibility

(This working group was not held).

Assessing individual risk factors

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Table 1. Summary of risk factors that should be assessed in studies, potential limitations and suggestions for best collection of each risk factor.

	What do we need to know	Potential limitations	How can we advance
NSAIDs	-Local suppliers -Frequency of use -Way of using them (like diluted in fluids: water, juice etc or in addition to vitamin B complex) -Prescriptions. -When do they take them (before, during or after work; before having pain or after) -Why do they take them, for "prevention" as a surrogate of vitamins, or as pain killers -Providers (companies, local sellers/distributors) To understand exposure levels it is advisable to use some qualitative methods before hand, in order to get ideas of type, frequency, ways, if it is work related and reasons for taking,	-Recall bias Mostly subject to self medication, -Possibility of not getting the information because **of fear** of being connected to the disease	A way of getting more information before deciding what and how to ask is doing community based participatory research together with key people from the communities (qualitative/anthropological research) to create a good environment for getting the information

	What do we need to know	Potential limitations	How can we advance
Nutrition	-We must take into account that we have disadvantaged populations with potential low birth weight which means reduce numbers of nephrons -Follow up studies since delivery, (other options, feasibility could be a hindrance) having access to registries, to get info of weight at birth. -Another option is a study of stunting as a surrogate of low birth weight. If we want to know about general aspects of dietary intake -It is not adequate to ask of dietary intake the day before or the week before due to a recall bias. -Body Mass Index information to know nutritional status is safely obtained in the fieldwork with a proper scale. The measurement in this case should be in the morning.		If we want to know nutrient current consumption then we should focus on what we want to know, i.e, soft drinks consumption for fructose intake, and not the entire food frequency ----Questionnaire

	What do we need to know	Potential limitations	How can we advance
Alcohol	-Information about suppliers -Type of alcohol, (legal or illegal) -Pattern of alcohol consumption through ethnographic study and using participatory action research to involve the community to first understand the habits, alcohol use frequency, times, if they drink during work (lunch time, after work) -Register information to calculate grams of alcohol to allow comparison -Consumption of homemade alcohol	There is a social stigma reporting alcohol consumption, underreporting due to connection with the CKDu	Group interviews, key informants interviews, anthropological studies
Other Exposures			
Smoking	-Habits with the usual questions and calculating pack years -Measure urinary cotinine could also include exposure to secondhand smoke.		
Drug use	Illegal Drug consumption among exposed population, use and abuse of legal drugs	-Safety problem especially in areas with high risk with drug dealers -Subject to selection and information bias	Tests of urinary metabolites for cocaine, marihuana, amphetamines, when is feasible
Exposure to sugarcane ashes in the environment distributed in the vicinity Dioxins and silica	The potential as a contaminant to affect the kidneys, both for workers and the neighborhood. Important the content evaluation of the ashes.	-Time for measuring the contaminant and exposure -Appropriate methods for lab analysis	Performing a study proposal for a community study that includes workers and their families during zafra (harvest) season
Use of homemade remedies (herbs) and medication	Habits of home remedies and medication to keep up their performance, and treat dehydration or heat stroke		Using observation through anthropologist specialists

	What do we need to know	Potential limitations	How can we advance
Habits to handle heat stroke	Self-medication, home remedies, visit to doctors, or health units		Using qualitative methods
Habits to keep themselves able to work	Hours working, resting time, drinking water, energizers, alcohol especially beer drinking, playing baseball or football, coffee to keep themselves awake or to "treat" dehydration or heat stroke		Using qualitative methods
Child labor	History of child labor using a question of age starting work paid or unpaid, duration and intensity		Include this type of questions in a questionnaire, a population study that includes the all possible age groups

Important: To perform a regional study to allow comparison among countries.

Assessing exposures to pesticides and metals

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Objectives

a. Consider the evidence for exposure to pesticides and to metals to explain epidemics of CKDnT
b. Identify the best methods to measure and quantify these for use in population and experimental studies and how to assure validity of measures in the field and in an experimental setting.

Output

a. Identify which pesticides and which metals are a priority for consideration in studies of CKDnT:
b. Identify how to quantify exposures.

Metals

Which metals are a priority for studies of CKDnT?

The present knowledge of the nephrotoxicity of metals is summarized elsewhere in this report. In brief, Cadmium (Cd), lead (Pb) and uranium (U) exposure are potential risk factors for decreased renal function and may at high exposure levels also cause acute clinical disease. On population level, the margin between dietary Cd exposure and subtle tubular effects may not be sufficient, especially not in populations with a high consumption of rice. There is, however, a lack of base-line data on cadmium, lead and uranium exposure levels in Central America, both in the general population and in occupational populations at risk of CKD. For inorganic arsenic (As), which in contrast to organic As has a well -known toxicity profile, no firm evidence of nephrotoxicity has been established.

The present sparse data from populations at risk for MeN, emanating from the Boston University investigations in Nicaraguan cane workers and unpublished data from sugarcane cutters in El Salvador presented during the workshop, have not indicated exposure to Pb and Cd at levels compatible with renal damage, taking existing dose-response relations into account. Similarly, the hitherto published data from Sri Lankan investigations do not indicate heavy metals as probable risk factors for the epidemic of CKDnT.

However, there is clearly a need for an extended monitoring of heavy metal exposure, both in the general population and in defined risk groups for CKD. This is especially the case for Cd, Pb and inorganic As. Also, monitoring of metal levels in drinking water is needed, especially in locations where the bedrock may contain metals that can be dissolved in the ground water. The primary reason for this recommendation is precautionary, since exposure to Cd, Pb and inorganic As have well-known extra-renal adverse effects.

How to assess exposure to metals?

Environmental monitoring should be performed to understand sources and routes of exposure, in particular via drinking water and food (e.g. rice, and other important dietary components). The use of biomarkers for heavy metals in body fluids and other tissues has a long tradition in occupational as well as environmental exposure monitoring. We here refer to the extensive biomonitoring literature for information on the consideration of suitable matrices and the correlated kinetics (i.e. which time period of exposure is reflected by the selected tissue), correct handling of samples to avoid contamination, and the accuracy of different analytical methods. Notably, international control programs exist for quality control, and should be adhered to.

In cross-sectional investigations measuring exposure and effect simultaneously, not only the understanding of the biomarker kinetics but also the concept of reverse causation has to be considered. This may also be a problem in case-control studies. However, such studies can be valuable for base-line exposure monitoring, and for time-trend investigations.

Pesticides

Which pesticides are a priority for studies of CKD?

Workgroup participants agreed that it is unlikely that pesticides can explain the epidemic of MeN in Mesoamerica. Pesticide and agrochemical exposures may possibly play a role in the CKDu epidemic observed in Sri Lanka, but there is a need to investigate other potential risk factors related to agricultural work, such as heat stress. Pesticide intoxications may be associated with acute as well as chronic CKD, possibly because due to non-specific mechanisms of action, but cannot explain the current epidemics.

Yet, it is necessary to study pesticide use and exposure in historical and current context. Based on the results of recently performed studies, herbicide exposure should be studied in more detail, in particular, glyphosates, paraquat, and 2,4-D. The past use of toxaphene should also be taken into account. Also, in sugarcane production, glyphosates have been aerially sprayed to mature cane, and may have caused relevant environmental exposures. As pesticides from different producers may vary in quality and added substances, it is necessary to study not only the active ingredients, but also the pesticide formulations and the toxicity of additives and possible contaminants such as cadmium.

How to assess exposure to pesticides?

Historical and current pesticide use should be studied by constructing pesticide crop use matrices. Such matrices can be constructed using e.g. pesticide import data and by interviewing agronomists and farm managers. IRET has long-standing experience that can be shared. It is also likely that large farms have registers of pesticide use. Collaboration with governmental agencies should also be used for data collection. By mapping crops, and pesticide use by crop, in relation to the prevalence of CKD, contrasts over time and space can be assessed.

On group and individual level, the use of questionnaires is common, but often the results are of limited quality, and not possible to compare between studies.

Environmental pesticide monitoring of air, dust, biomaterials, and water should be performed taking the timing of sampling in relation to agricultural activities into consideration. Proper sampling and good analytical quality is a prerequisite.

Personal airborne and dermal exposure assessment can be performed in occupational settings. For a very limited number of pesticides there are also biomarkers of exposure (e.g. metabolites in urine), usually reflecting only ongoing or recent exposures. Thus, the same concerns about timing of sampling and biomarker kinetics as for the metal biomarkers are valid.

In summary, life-time exposures to pesticides should be assessed using mixed data collection methods (registry data, interviews and questionnaires, environmental monitoring, biomonitoring). Finally, to answer the questions whether pesticides play a role in CKD, research priorities should be set at a regional and international level. It is recommended to develop a core module for assessment on pesticide exposure that can be used for regional, national and international comparisons.

Assessing exposure to environmental heat load/ dehydration and workload

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Objectives

a. Consider the essentials of field assessment and quantification of heat load/dehydration and workload in both short and long-term studies and how to assure validity of measures in the field and in an experimental setting
b. Propose priority measures of heat/ dehydration and of workload that are necessary to include in population studies or to examine in laboratory investigations.

Heat exposure

The following methods were discussed for assessing heat exposure. Each has benefits and challenges that should be evaluated based on the study question, design and population.

Table 1. Heat Exposure Factors and Methods.

Factor	Method	Validity	Appropriateness	Comments/Recommendations
Internal heat production	Gastro intestinal temperature (via an ingestible telemetry pill system)	A valid and reliable measure of body core temperature for field-based measurements.	Expensive May be unacceptable to some individuals/ populations. Consider contraindications for safe use of the pill. These include reusing a pill, having a MRI with a pill ingested, choking hazard for small children and chewing the pill.	Any field studies using gastrointestinal pills might also measure tympanic temperature and report their findings widely to explore validity of tympanic measurements and modeled estimates of body core temperature (Buller et al 2013).
	Tympanic temperature (via infrared thermometer or tympanic thermistor)	Infrared tympanic temperature measurements are not currently accepted as a valid measure of body core temperature.	Less invasive than a gastrointestinal pill, although more difficult to get reliable readings (i.e. due to the shape of the ear and ear canal, user technique etc.).	At this stage, tympanic temperature should not be used in isolation to describe body core temperature, but could be used in addition to other methods in an attempt to further validate this measure.

Factor	Method	Validity	Appropriateness	Comments/Recommendations
Local Climate	Modeled estimates (Heat stress indexes such as WBGT, Humidex, NIOSH Heat index)	WBGT is one of the most widely used heat indexes, but is expensive to measure and requires being onsite. Existing data from previous studies makes data easily comparable to other countries/ job tasks. "Permissible" heat exposure threshold limit values are often published using WBGT.	Humidex and Heat index are user-friendly and can be more easily understood by workers and employers. WBGT is appropriate for initial studies, but not practical for day-to-day monitoring long term. In all cases, it is obligatory to measure as a minimum temperature and humidity. Dry temperature measures alone are not sufficient to calculate a meaningful heat stress index.	It is important to know and report the assumptions being made when calculating heat stress based on an index: i.e. clothing, wind velocity. It is also valuable to have an estimate of the metabolic rate for the particular job task being examined. Interpretation of WBGT should be done according to standard protocol (i.e. not interpreted only on an hourly basis) Acclimatization, acclimation and cardiovascular fitness are important factors influencing heat tolerance and are potentially accounted for in some heat stress indexes.

Factor	Method	Validity	Appropriateness	Comments/Recommendations
Local Climate	Portable weather stations	Having complete weather data is helpful in initial assessments of heat exposure in a specific working population.	Some technically "portable" weather stations are cumbersome and generally expensive and therefore not always appropriate for field monitoring. If the possibility exists to have the station in place for a long period of time, it could provide helpful data.	Relatively small scale studies to compare local field assessments to airport weather data could be useful. These data are relevant both from a historical and future perspective in relation to understanding worker health in relation to climate change. Studies that map heat index change over time would be useful.
	Small portable temperature/ humidity loggers (eg: HOBO data loggers)	There are limitations to only using temperature and humidity to estimate heat exposure, but individual-level data can be very useful.	Would provide data on temperature and humidity conditions during transport to and from the field and also during the night. These data might be important for fully understanding heat exposure.	Personal-level data can be compared to field-level WBGT data and publically available geographical grid level weather data.
General Climate	Airport weather stations	Airport weather stations data can be accurate and readily available, but they do not necessarily reflect the specific conditions of a particular workplace.	Attractive because they are readily available and would enable larger spatial and temporal comparisons (i.e., across decades, between countries or around the globe.)	Airport weather data should be compared to locally collected data in a workplace before using it to calculate heat exposure.
	Global climate databases (NOAA)	Generally accurate and detailed data.		Studies to compare general climate data to locally collected data would be useful.

Dehydration/fluid balance

Understanding the amount of fluid consumed by workers affected by heat and heavy workload is essential, yet quite difficult to assess accurately. Some experience and insight has been gained by recent studies that have attempted to measure fluid consumption. Difficulties and potential solutions to measuring dehydration and fluid balance were discussed.

Table 2. Dehydration/fluid balance measures.

Measure	Difficulty	Possible solutions
Fluid consumption	Worker recall about the volume of fluid they have consumed is notoriously inaccurate and workers often have trouble knowing how much their cups or water bottles hold.	Using a questionnaire with pictures of cup and water bottle sizes.
		Workers are generally able to recall a number of something consumed. For example, they are more likely to accurately remember that they consumed 2 "bolis" than to know how many liters of water they consumed. If workers use a standard size water bottle, they may be more accurate in reporting how many bottles they have consumed. For increased accuracy, the bottles can be visually inspected or weighed pre and post shift; and fluid distributed during the shift can be observed and recorded.

Measure	Difficulty	Possible solutions
Fluid balance - weight loss	Changes in body mass is a reliable and valid measure of sweat loss and dehydration (i.e., % change in body mass is used to describe level of dehydration in literature). However, weighing scales can fail in the field due to heat, uneven terrain or direct sun.	More expensive scales are reported to perform better in the heat. Researchers should plan to calibrate scales regularly in the field.
	Workers must be weighed wearing the same clothes pre and post shift. Ideally, workers are weighed nude or in underwear, but cultural and field conditions often make this impossible.	
	Food and fluid consumption during a shift must be accurately recorded for all participants in order to interpret changes in body mass data. Researchers should also ideally know how many times and how much participants urinated. Some of the Central American studies that have tried this report workers who were unable to urinate at the end of the shift.	Workers generally do not recall or self-report food and fluid consumption accurately enough for study purposes. Direct observation is much more effective.
	In the case of sugarcane cutters, soot, dirt and sweat in clothing will add to weight post-shift.	

Measure	Difficulty	Possible solutions
Fluid balance - biomarker	USG is debated as a valid measure of hydration, but remains a rather easy and inexpensive indicator. USG should be interpreted with other biomarkers. It is also unclear whether USG is valid in workers with reduced kidney function.	Pooling data and "lessons learned" from field studies could allow us to create a "living" shared protocol for measuring fluid balance.
	Changes in plasma volume can be estimated from changes in haemoglobin concentration and hematocrit using the previously established calculations (Dill & Costill 1974)	It is useful to measure pre-shift, post-shift and the morning following the shift when looking for biomarkers until more research confirms the ideal timing of measurements. Existing data suggests biomarkers may be most informative the morning after a shift (after sleep).
	Urine and serum/plasma osmolality is worth testing. Serum/plasma osmolality reference values can be used to quantify hydration status and water-loss dehydration.	
	Some relatively new options such as postural blood pressure might be helpful. The US Army has data on the expected blood pressure changes from laying, sitting and standing.	Creating a standard protocol and validating it in different study populations might help determine whether this is an appropriate and valid measure.
Salt loss	Electrolyte loss remains relatively understudied for working populations. Of note, endurance training and heat acclimation/acclimatization dilutes sweat and preserves electrolytes in extracellular fluid.	One possibility might be to measure electrolytes in sweat. This has not been done yet by any research groups.

Workload

It is essential to understand workload in CKDnT affected populations; however the methods for achieving this are varied. The pros, cons and possible solutions to common difficulties were discussed. These are summarized below.

Table 3. Measures of workload.

Measure	Pros	Cons	Common difficulties and possible solutions	Remaining questions and future steps
Heart rate	A very useful tool in measuring workload objectively	Cardiac drift occurs with heat stress, i.e., heart rate increases beyond metabolic demand due to a temperature effect.	Purchasing the correct equipment (eg. Polar watches) can be very confusing. It is important to know whether the equipment is coded or encoded and whether there will be logger interference when workers are close together. It is also essential to know how often it will log data and for how long. Many models will only give a minimum, maximum and average, but ideally, researchers should be able to log heart rate at least hourly.	The US Army has a model that uses heart rate to estimate changes in core temperature. This might be worth investigating further (Buller et al 2013).
	A recent US army model (Buller 2013) estimates change in body core temperature from heart rate.	This model is relatively new and has not yet been widely validated.	To date, this model has not been validated in sugarcane cutters against more direct measures of body core temperature.	
	Monitors with a wristwatch and chest band easily used in the field.	Can be expensive and may be interference between workers, especially if researcher wears the wrist monitor.		

Measure	Pros	Cons	Common difficulties and possible solutions	Remaining questions and future steps
Accelerometers	Relatively inexpensive and objective tool.	Placement of accelerometers for tasks such as cutting sugarcane is not standard. For example, placement might determine whether they can accurately be used to measure cutting versus walking. ActiGraph equipment seems to be the most commonly used.	Sharing experiences would be helpful to standardize protocols.	It might be interesting to experiment with placement of two accelerometers on the machete and one on the worker's trunk/wrist to determine more specific information about the task of cutting cane.
Observational	Inexpensive method that does not require the purchasing of equipment.	Workload classifications are very general, leading to many job tasks with the same metabolic load.		

Measure	Pros	Cons	Common difficulties and possible solutions	Remaining questions and future steps
Productivity (ie number of feet cut, baskets collected or tons cut).	Theoretically, productivity should decrease with increased heat exposure and dehydration. In tasks paid by the piece/weight, this can be relatively easy to measure.	Assumptions must be made to be able to compare different days within the same work group and to compare different working groups or different jobs. (i.e. if cane is hard to cut one day and easy to cut the next day, using "productivity" as an indicator may be misleading.	When observing cane cutting, the following considerations are important: How tangled was the cane? (Workers are generally able to say whether the cane was good (easy), normal or bad (difficult)). Variation in cane weight (The workers will be paid by meters cut and the weight of the cane once it is taken to the mill. The weight can vary considerably depending on the variety of cane as well as how long it was in the field. It is necessary to know the age, weight and body mass of workers to interpret metabolic load. Videotaping the work is recommended to help with the interpretation of accelerometer data.	

Priority research and actions

The following actions and research initiatives are recommended as top priority:

1. Creating shared protocols and reporting quickly on data and lessons learned, especially with regard to validating (or developing a correction model for) less expensive and less invasive methods.

2. Whenever possible, researchers should use more than one measurement to help with validation (eg. report both individual-level heat monitors as well as WBGT and airport data or report both gastrointestinal pill and tympanic temperature).

References

1. Buller, et al., Estimation of human core temperature from sequential heart rate observations. Physiological measurement 2013, 34, 781 [see also: http://www.usariem.army.mil/index.cfm/modeling/cbt_algorithm]

2. Dill and Costill. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. J Appl Physiol 1974, 37, 247-248.

Consideration on infectious agents

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The Working Group on Infectious Agents was charged to consider evidence for infectious (bacterial, parasitic or viral) etiologies for CKDu and how these might be assessed in field studies. Based on these considerations the group was asked to:

Propose which, if any, infectious agents are important to further assess in population or laboratory studies of CKDnT

Knowledge and knowledge gaps

The group discussed the evidence base for an infectious agent role in the etiology of CKDu and gaps in that evidence base. In advance of the working group a literature review in PubMed identified 462 articles (39 non-English) by using the following key words in the search: infection, "chronic kidney/renal failure/disease"; cause, etiology and adult. A summary of the findings from that search indicates that a) there are infectious complications of persons with established kidney failure as a consequence of immunosuppression, b) there are renal manifestations of infectious disease, and c) that infectious diseases are associated with (a consequence of) kidney failure.

In sum the group judged that infectious diseases should be considered an unlikely cause of CKDu but could contribute to the worsening of clinical progression for those with chronic kidney disease. Agents thought most likely to contribute to the worsening are Leptospira, Hantavirus, Dengue, and West Nile virus. More research is required to improve understanding. This research would be facilitated by targeted studies of blood samples of those with CKD (both serum and whole blood) and of tissue samples (kidney and bone marrow biopsies). For these studies to be a success it is critical that good comparison groups be selected and evaluated in the same manner.

Recommendations to move forward

1. The primary recommendations from the workgroup

- Strengthen collaborations among groups of researchers both those investigating infectious agents and those directing attention to etiologic studies of CKDu
- Studies of infectious agents require testing of blood, serum, urine and tissue samples with careful attention to proper standardization of collection, management and examination of the biologic materials
- It will be necessary to coordinate with hospitals and families in order to obtain proper tissues and samples to be tested
- The use of antibody testing remains a mainstay of this research but there is a need to continue efforts to develop and apply new tools for biological testing and detecting agents that can improve upon or expand the information available from antibody testing alone
- Case studies continue to offer insights but a priority should be place on establishing research based in cohorts to understand burden and natural history of the role of infectious agents in CKDu.

Understanding the mechanism of Mesoamerican nephropathy - Theory

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Output

Characterize the most promising hypotheses and propose laboratory and/or field studies to confirm or refute.

Report

A wide variety of etiologies have been proposed to explain the cause of Mesoamerican Nephropathy in Central America, including exposure to herbicides, pesticides, heavy metals (cadmium, arsenic, lead), toxins *(Aristolochia*), drugs (NSAIDs), infections (Leptospirosis, Hanta virus), metabolic causes (hypokalemia, hyperuricemia), and the effects of strenuous physical labor in the presences of heat stress and recurrent dehydration.

To date, heat stress due to high ambient temperature and strenuous work have been identified as important factors. These factors, in combination with dehydration may lead to reduced renal perfusion and renal ischemia which could explain the histopathological findings found in renal biopsies; chronic tubulointersitial changes and glomerular ischemia with glomerulosclerosis.

However, several mechanisms could indeed contribute to the ischemic renal damage (Figure 1);

- *Increase in body temperature:* Physical activity generates endogenous heat and higher body temperature, which adds to the heat from the high environmental temperatures.
- *Uric acid:* Serum uric acid levels rise during the workday due to the increased release of substrate (purines) as a product of the intense muscle activity associated with strenuous labor. Coupled with the heat stress experienced, this may lead to uricosuria. A transient state of volume depletion ensues, producing a fall in kidney perfusion and high demands on tubular reabsorption, with the consequent activation of several compensatory mechanisms (systemic vasopressin and local activation of the aldose reductase-fructokinase pathway in the renal tubule). Then, uricosuria in the concentrated and acidified urine may form urate crystals.
- *Salt depletion and RAAS activation:* Strenuous work in high ambient temperature results in sweating and loss of salts that, in combination with dehydration, may activate the RAAS system and result in intrarenal vasoconstriction and hypokalemia. Activation of RAAS is supported by the low sodium and potassium levels often found in MeN patients and may also present in workers doing strenuous work in these environments..
- *Intake of pain killers:* In dehydrated patients, intake of NSAIDs could further impair renal blood flow and may further contribute to the renal injury.

Studies recommended to confirm the hypothesis

Experimental studies: Are important to evaluate the role of uric acid and heat exposure as mechanisms for the development of CKD.

Intervention studies: To optimize water intake (ongoing studies in El Salvador), to optimize rehydration (water, salt and glucose) and to optimize rehydration and treat with urine alkalization and xanthine oxidase blockage. Heat control by "rest and shade" should be recommended in all studies. The ultimate outcome is stable eGFR. Monitoring of the following parameters would be valuable: Medication, heat stress symptoms, hydration status, plasma electrolytes , plasma and urine uric acid, and RAAS, biomarkers for tubular injury.

If possible, studies of urine; volume, osmolality electrolytes / 24 h would be informative.

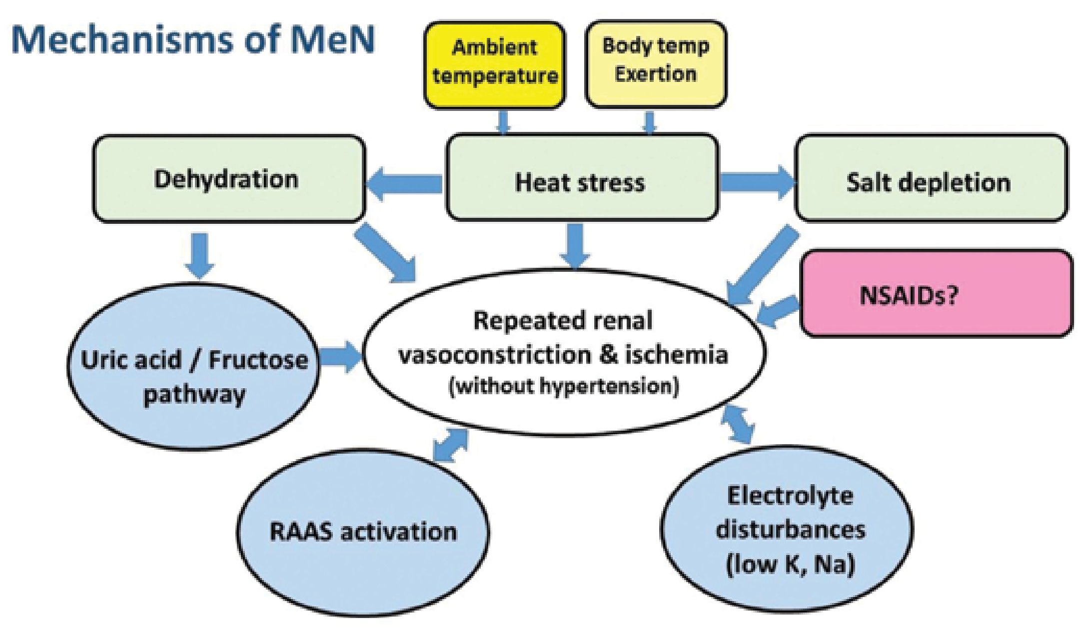
Biopsy studies: Biopsy studies in early stages of the renal disease, if possible in the acute phase, would add valuable information about the acute injury and the possible presence of urate crystals in the tissue.

Studies needed to find out if CKDu found in other endemic areas represent MeN

The group discussed possible causes of CKDu in Sri Lanka where the researchers in Sri Lanka have considered a combination of toxic chemicals and heavy metal as the most relevant contributing factors to the CKD found in that area.

To find out if CKD of unknown etiology in other endemic areas, e.g., Sri Lanka, is the same disease as MeN it is important to perform renal biopsies on carefully selected patients. Reduced eGFR (and not proteinuria) should be used as inclusion criteria and patients with diabetes and hypertension should be excluded. Clinical characteristics should be identified and blood and urine samples should be collected at the time of biopsy. Standardized questionnaires would be of great value (see summary of Working Group on Developing Central Elements for a Core Questionnaire.

Figure 1. Proposed mechanism of chronic kidney injury in Mesoamerican nephropathy.



Developing central elements for a core questionnaire

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During its discussions, the Working Group covered the following areas:

1. Rationale for a core questionnaire
2. Topics to consider for inclusion
3. Methods for testing and evaluation
4. Next steps

Rationale

Participants identified a number of advantages of developing a core questionnaire, including:

1. Enhancing comparisons of study findings across different populations, including allowing for pooling of data across studies.
2. Encouraging the conduct of studies in areas where there are reports of MeN but little data.
3. Initiating a process that would produce a higher-quality questionnaire because it would

- **a.** Allow for a systematic consideration of topics that should be prioritized,
- **b.** Identification of validated instruments and questions where possible, and
- **c.** A centralized, efficient process of testing and evaluation, with special attention paid to important topics for which good data have been difficult to obtain by questionnaire. Cited examples included agrichemical exposure, heat stress and hydration, and medications (pharmaceutical and herbal).

At the same time, working group participants noted that researchers might be interested in different populations and questionnaires might be administered in different settings, both of which could impact the types of topics that might be considered most relevant. Community residents, workers, and patients were the main groups identified. Not only might the questions differ for these groups, but the amount of time available to ask questions could range greatly depending on the setting. For example, questionnaires administered at a worksite might need to be limited to 10-15 minutes or less, while community-based questionnaires administered at participants' homes might extend for an hour or more.

Working group participants also noted that the design of the study also could have an impact on the type of information gathered, particularly whether only a single (cross-sectional, case-control, or retrospective cohort study) or multiple (prospective cohort study) encounters were anticipated.

While recognizing this variability, there was agreement that certain topics would be of common interest across groups and that a core questionnaire would be a useful template, understanding that different researchers would want to add or modify certain questions. Rather than try to consider different uses, the working group participants agreed that it would be most useful to start with the elements of a questionnaire that would be used in a cross-sectional/case-control study of community residents in which the assessment of factors associated with elevated creatinine levels was of primary interest.

Topics

Working group participants struggled with the balance between the desire for brevity and at the same time for sufficient information. This conflict manifested itself in both the number of topics and the number of questions for each topic. An example of the latter concern was the issue of work history, which everyone agreed was an important topic. Discussion centered on the question of how much detail was needed to get a measure of work history that would provide useful information for assessment of an association with elevated creatinine level. Participants did not reach a conclusion, but this question was recognized as an important issue for future consideration.

Given time limitations and the fact that this meeting was the first time most working group participants had the opportunity to consider the idea of the core questionnaire, it was decided that it would be most useful for participants to focus on suggesting a range of possible topics and not try to narrow down the list. The list of suggested topics is included in the table at the end of this summary.

Testing and evaluation

Working group participants recognized that formal validation studies were unlikely to be undertaken, but that efforts should be made to make the questions as accurate and useful as possible. Suggestions included:

1. Use validated questions when possible, while recognizing that it is important to consider the population in which the questions have been validated, as validity can be population-specific.
2. Circulate draft questions within CENCAM, so that the experience and perspective of the broader community of researchers has a chance to be incorporated into the questionnaire.
3. The questionnaire should be piloted with community members in different locations to test reliability. In addition, the technique of interview probing should be used to assess how community participants' understood the question in order to identify problems with wording.

It was also recognized that a core questionnaire would still need to be adapted based on the knowledge of the researchers in consultation with the study participants to account for differences in terminology and culture between and within different countries.

Next steps

The working group participants suggested the following steps:

1. Set up a CENCAM task force
2. First focus on one common scenario: baseline/one-time questionnaire of adults at work or in community. Consider longer and shorter versions.
3. Inventory questionnaires used to date in study of MeN, and obtain input from researchers regarding more or less successful questions.
4. Search more broadly for questionnaires that can provide assistance for topics that have proven to be difficult to obtain good data.
5. Develop, circulate, field test, and revise proposed core elements for questionnaire

Table 1. Suggestions for elements of a core questionnaire.

Topic	Potential Elements	Considerations
Demographics	Sex, age, height, weight, socioeconomic position (SEP), access to medical care	What are appropriate SEP measures? USAID questionnaire uses index of running water, roof materials
Residential	Years, migration, water source, sanitation facilities, agrichemical use	
Occupation	Industry/crop/job/tasks (current, past), age started working, labor migration, years, hours, days per week, employment relationship, form of compensation (hourly, piece rate), personal protective equipment	
Heat stress	Level of exertion/sweating, symptoms (timing, duration, frequency, episodic vs. chronic)	
Hydration	Type (at work/not at work, amount)	Visual aids would help for amounts. What is an appropriate recall period?
Agrichemicals	Location (Work/not at work); years, days/ year, age started; ever intoxication; planes spraying	Focus only on agrichemicals already identified as potentially nephrotoxic?
Medical history/ symptoms	CKD (personal and family), diabetes, hypertension	
Medications	NSAIDS, other pain relievers nephrotoxic antibiotics, pyridium; chronic vs. episodic use	Visual aids would help for pharmalogical medications. What is the appropriate recall period? Are herbal medications important for etiology of MeN? How can they be ascertained in a brief questionnaire (Y/N question, followed by open-ended response for specific names)?
Behaviors	Smoking, alcohol	

Approaches to intervention

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Introduction

As we come closer to identifying the underlying cause of the Mesoamerican nephropathy epidemic, we have reached the point where it is beyond reasonable doubt that the issue lies within the occupational setting. Irrespectively all agree that manual cane-cutting is a high-risk job with environmental and occupational hazardous exposures that could be tackled through interventions. Participants in this workshop agreed that we do not have to wait for research to come out to improve working conditions.

Interventions can take place at several levels in society and business. They could also have long-term as well as short-term objectives. It is important to try to stop the epidemic as soon as possible and we also need to figure out how to tackle implications in the long run. Structural reform of business is under way and intervention strategies have to address several levels of society. Figure 1 depicts the macro, meso and micro level of intervention and its potential impact. On an international level, interventions could be aimed at trade agreements, fair trade programs

etc. that could change the working live for many workers across several countries at the same time. On a national or industry-wide level, policy regulations, engagement of national governmental bodies such as the min. Labor, Health, Environment etc. could result in intervention through legislation regarding work practices, child labor, pesticides, minimum wage, etc. The national and regional sugar industry could also be target for business model interventions aimed at identifying the competitive edge and investing in modernization. If changes are not achieved industry-wide, individual companies could take the lead and show how modernization, interventions along the value chain, vocational training for workers during transition process and other interventions could increase productivity and revenues. Finally, on a worker-level, there are several interventions that could be of great value if proven successful and disseminated to a wider audience. Education and sensitization regarding pesticides, heat and ergonomics could be important although individualizing these problems won't have big impact.

Intervention priorities

1. Mitigate Heat Stress

A further development and evaluation of Water.Rest.Shade components and different modes of the program in order to evaluate best practices in each situation. Also a need to develop suitable re-hydration formulas and develop common protocols for evaluation of heat stress and hydration.

2. Innovation and education

Pesticides—how and when to apply, good practices

Ergonomics—bring in field engineers

Heat Stress/Dehydration - Intelligent textiles—fabric that cools

Total worker health—medications, nutritional interventions

3. Policy intervention

Comprehensive legislation on import/export of pesticides.

Education and training programs to ease the transition when mechanization happens.

4. Re-inventing business models and economic impact.

CENCAM lacks health and business economists who can evaluate the cost-benefit of interventions on both company and societal level.

Key components for successful interventions

- Good planning and communication with all stakeholders.
- Intervention on multiple sites to protect from unforeseen events such as bankruptcy or sudden changes of heart in individual companies or governments.
- Testing methodology. Development of a living lab where interventions could be tested and interested parties could test live intervention.
- Build on knowledge from other disciplines such as sports medicine, engineering, sociology etc. Interdisciplinary research is key.

Table 1. Possible interventions at several different levels in society.

	Worker	Company	National/ industry	International
Legislation			X	X
Modernization		X	X	X
Hygiene&Sanitation	X	X	X	
Economy		X	X	
Wages		X	X	
Pesticides	X	X	X	X
New technology	X	X	X	X
Heat/Dehydration	X	X	X	X
Efficiency	X	X	X	
Vocational training	X	X	X	
Education	X	X	X	
Medical Surveillance	X	X		
Ergonomics	X	X		
Nutrition	X	X		

Understanding macro factors

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Objectives

Since epidemics exist in a social context, we considered how we can study the social context in which MeN occurs, including socio-economic status, migrant labour patterns, and other factors affecting community health.

Summary

Exposures and the development of MeN occur in a context that involves working conditions, and the biogeochemical environment, as well as the immediate, local and global context and the economic and political realities. Understanding of the context and the interaction of the different factors that influence the development of MeN can lead to improved study designs, interpretations and recommendations for change. For example, knowledge of the particular social and economic pressures that influence working conditions and/or the evolution of MeN can help us to ask the most appropriate questions with respect to causes, and with respect to policy.

Macro factors

The working group considered various factors that could be considered as macro factors. Here, they are grouped from the most proximal to the worker to the most distal or global. Because of the high prevalence of MeN among sugar cane workers, we use this as an example, but it can apply to other occupations and/or environmental conditions where MeN may develop.

- **The worker:** While most of the workers are men, there is a growing number of women that are working in sugar cane. In addition to the biologic differences that may influence the development of the MeN, women and men have different social roles and possibly different co-exposures, life trajectories and medical history that may be relevant to MeN.
- **The workers' home environment:** The worker's home constitutes the most immediate physical and social environment. The proximal physical environment can be beneficial or harmful to health depending construction materials, its situation in an area conducive to insect breeding or to heavy smoke during sugar cane burning, as well as access to potable water and healthy food. The immediate social determinants of health likewise play an important role in the capacity to recuperate from workplace stress and to overcome developing illness: these include family psychological and physical support, crowding, gender relations, income and lifestyle. For example, after a day's hard labour, having another person care for your needs - usually but not always, a women (mother, daughter, sister) who cares for both men and women workers - may mitigate, at least partially, the harm done to the body's attempt to adapt to extreme conditions.
- **Worker status:** Workers may be regular or contractual employees of a company, self-employed or in a cooperative, with regular or migrant status. In some instances workers are hired by a foreperson on a daily or weekly basis from a group seeking employ-

ment. Those who are most fit or appear to be most fit are more likely to be selected.

- **Work organization and co-exposures:** Work organization includes the work pace - often determined by the means of remuneration (piece work, quota system and/or salary) - the area allotted for water, rest and shade, as well as the physical dimensions and organisation of the working area, which for sugar cane, can facilitate, or not, as the ease of cutting. Pollution from pesticide use, silica and burning can further influence overall health and renal functioning. Indeed, both direct and indirect work-related factors can potentially contribute to or accelerate the development of disease.
- **Local ecosystem:** For outdoor work, the local ecosystem, which depends on the global ecosystem, is affects the ambient temperature and humidity. Global climate change, which in local tropical coastal areas translates into increasing mean and maximum temperatures, intensifies heat stress, particularly when the body is functioning at its limits of adaptation and internal heat production is high from physical exertion.
- **Health services and access:** In many areas, health services are minimal and sometimes absent. Local health personnel may not be knowledgeable about MeN, but may have useful information about the type of signs and symptoms that they observe. In some instances, there may be traditional medicine providers, who may also have knowledge of ailments and the use of traditional remedies. Difficult access to health services often translates into waiting before one can no longer work before consulting with the health services.
- **Local laws, regulation and implementation:** These also shape working conditions and health outcomes. The Global Agricultural Information Network (GAIN) report of the USDA Foreign Agricultural Service[8] contains the following: *"A national sugar law for commercialization, production, and distribution of sugar is an important component to the reengineering process that the industry has undergone. In addition, assisted by (mostly) attractive prices and additional access to the U.S. market, the sector seems to be recovering financially after facing debt complications due to natural disasters, high transportation costs and lack of government policies to assist sugarcane growers. Ultimately the success of the industry will depend on compliance with the sugar law by all the stake holders, continued improvement in sugarcane and sugar yields, and increased diversification into additional energy co-generation projects and an ethanol law that encourages investment. However, increased crime rates including extortions are of major concern to the sector."* Knowing how a local industry complies with the laws and regulation, and how they are implemented, can help us to understand the working conditions and improve ergonomic observations and/or questionnaire design.
- **Economic and political forces:** The economic and political forces that drive the local, national and global economies likewise influence workers' health. Commodities, like sugar cane are subject to market pressures and fluctuations, which, in turn, affect prices, production and working conditions. For example, the report cited above indicates: *"Higher yielding sugarcane varieties, diversification of the industry into the production of energy and alcohol/ethanol, investment in milling equipment to improve sugar yields, and additional access to the U.S. market due to CAFTA-DR will all continue to benefit El Salvador's sugar industry over the next 3 to 5 years. Declining international prices and an expected El Nino weather pattern might bring stormy conditions."*

1. http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Sugar%20Annual_San%20Salvador_El%20Salvador_4-18-2015.pdf

- **International agreements:** International agreements bring in voices from around the world, including consumers that consider working conditions and workers health as part of "fair trade" policies. For example, in November 2013, Central America, signed a Trade Association Agreement with the European Union that provides access to up to 100,000 MT of duty-free sugar from the region[1]. Furthermore, Central America is negotiating a free trade agreement with Canada that could also affect the sugar industry[1]. Knowledge of the factors in play can be useful in thinking about how these factors affect working conditions (and thus inform our questionnaires on working conditions) and demands on production levels (and thus interpretation of results and possible recommendations). For sugar cane cutters, the international agreements on climate change mitigation may have a direct effect on their working conditions.
- **History:** An understanding of the different histories, including the history of the worker, the community, the region, and the country, as well as the history of the disease in this and other areas can further contribute to better a better comprehension of macro-factors that may influence the development of MeN.

Recommendations

The workshop proposed the following recommendations:

- More inter-disciplinary focussed research, which incorporates on a non-hegemonic basis, the natural sciences, social sciences, policy and economic research, as well as the health sciences into on-going and proposed field and clinical studies on MeN.
- An ecosystem approach, based on systems analysis, can be helpful in mapping out the pathways of how the various macro factors and their interactions may influence the development of the disease at different points in the continuum from health to disease state.
- Study designs that are iterative and incorporate space for interventions and evaluation of acceptance and efficiency. (eg water/rest/shade and cost-effective treatments).
- Gender and sex sensitive approaches that identify issues such as co-exposures, roles, living and working conditions, health status, home and outside care that are specific or similar for men and women.
- Participatory research where we can learn from communities' and stakeholders' knowledge and provide them with the means of changing their situation (empowerment)
- An ecosystem approach, based on systems analysis, can be helpful in mapping out the various influences and their interactions.
- We need to develop: (i) an overview of the essential elements of the social context which should be taken into account in field studies ; (ii) an overview of the role researchers can play in their amelioration ; (iii) recommendations on how to move forward to fill those knowledge gaps.

Understanding context

Since MeN is primarily an occupational illness, here, we place the worker in the center. The worker's home constitutes the most immediate physical and social environment. The proximal physical environment can be beneficial or harmful to health depending construction materials, its situation in an area conducive to insect breeding or to heavy smoke during sugar cane burning, as well as access to potable water and healthy food. The immediate social determinants of health likewise play an important role in the capacity to recuperate from workplace stress and to overcome developing illness: family psychological and physical support, crowding, gender relations, income and lifestyle. For example, after a day's hard labour, having another person care for your needs, usually but not always, a women (mother, daughter, sister) who cares for both men and women workers, can counteract, at least partially, the harm done to the body's attempt to adapt to extreme conditions.

A good portion of the waking day is spent in the workplace, where the primary determinant of MeN is the work situation and work organization. Workers may be regular or contractual employees of a company, self-employed or in a cooperative, with regular or migrant status. In some instances workers are hired by a foreperson on a daily or weekly basis from a group seeking employment. Those who are most fit or appear to be most fit are more likely to be selected. Work organization includes the work pace, often determined by the means of remuneration (piece work, quota system and/or salary), the area allotted for water, rest and shade, as well as the physical dimensions and organisation of the working area, which for sugar cane, can facilitate, or not, as the ease of cutting. Pollution from pesticide use, silica and burning can further influence overall health and renal functioning. Indeed, both direct and indirect work-related factors can contribute to or accelerate the development of disease.

For outdoor work, the local ecosystem, which is dependant on the global ecosystem is central to the ambient temperature and humidity. Global climate change, which in local tropical coastal areas is producing increasing mean and maximum temperatures, intensifies heat stress, particular when the body is functioning at its limit of adaptation.

The economic and political forces that drive the local, national and global economies likewise influence workers' health. Commodities, like sugar cane are subject to market pressures and fluctuations, which, in turn, affect prices, production and working conditions. For example, the Global Agricultural Information Network (GAIN) report of the USDA Foreign Agricultural Service[9], states that "Higher yielding sugarcane varieties, diversification of the industry into the production of energy and alcohol/ ethanol, investment in milling equipment to improve sugar yields, and additional access to the U.S. market due to CAFTA-DR will all continue to benefit El Salvador's sugar industry over the next 3 to 5 years. Declining international prices and an expected El Nino weather pattern might bring stormy conditions." Knowledge of the factors in play can be useful in thinking about how these factors affect working conditions (and thus questionnaires on working conditions) and demands on production levels (and thus interpretation of results and possible recommendations).

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Local laws, regulation and implementation also shape working conditions and health outcomes. The report for the El Salvador sugar industry sited above indicates : "A national sugar law for commercialization, production, and distribution of sugar is an important component to the reengineering process that the industry has undergone. In addition, assisted by (mostly) attractive prices and additional access to the U.S. market, the sector seems to be recovering financially after facing debt complications due to natural disasters, high transportation costs and lack of government policies to assist sugarcane growers. Ultimately the success of the industry will depend on compliance with the sugar law by all the stake holders, continued improvement in sugarcane and sugar yields, and increased diversification into additional energy co-generation projects and an ethanol law that encourages investment. However, increased crime rates including extortions are of major concern to the sector." Knowing how a local industry complies with the laws and regulation and how they are

2. http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Sugar%20Annual_San%20Salvador_El%20Salvador_4-18-2015.pdf implemented can help to understand the working conditions and improve ergonomic observations and/or questionnaire design.

History

- Gender roles and relations
- Health services and access
- Social security

Approaches to surveillance of MeN

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Randall Lou
Mathew Lozier
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Virginia Weaver
Elizabeth Whelan
Roy Wong

The Working Group on Surveillance was charged to prepare the following output:

Propose administrative, hospital, or community-based measures for case- based and population-based measurement of MeN and potential ways to collaborate between governments and between government and academia.

The group discussed the objectives of surveillance in general and as applied to the CKD problem present in Central America. The CDC definition of surveillance was accepted: "ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practices, closely integrated with the timely dissemination of these data to those who need to know (CDC, 1988)". It can be seen as the "cornerstone of public health practice" that provides the foundation on which to build successful prevention programs.

Surveillance is systematic; it is carried out using consistent methods over time. It is often continuous but may also be periodic. However, it should not be confused with one-time survey research efforts. Second, and perhaps most importantly, surveillance carries with it a responsibility for public health action. While the precise boundary between surveillance and intervention is subject to debate, it is widely accepted that the final link in the surveillance chain is the application of the data to prevention.

In the setting related to MeN, surveillance was seen as essential to:

- » Document the overall magnitude of the problem
- » Characterize the populations (defined by age, gender, race/ethnicity) at risk that merit special attention
- » Identify the work or jobs where intervention is most needed Identify individual workplaces (or areas within workplaces) where intervention is warranted
- » Characterize the illnesses, its causes and known risk factors that need to be addressed
- » Identify potential, previously undocumented risk factors that require further etiologic research

Surveillance across countries, particularly those with limited resources, is often very difficult. Surveillance might be focused only on established cases or it might include those where there is only a suspicion of a case. Depending on specified objectives, surveillance can be based on different levels of information ranging from suspicion of a case (does not require clinical confirmation) to certainty of a medical diagnosis. If surveillance definitions are well specified then these can be used selectively as needed to estimate burden, report characteristics of cases according to different definitions, describe populations likely to be at risk, follow-up of individual cases, or identify "hotspots" where a disease of interest is unusually concentrated. Where possible surveillance information can be stratified according to the specific criteria that cases meet ranging from possible and probable to definite.

Knowledge gaps

The working group discussed knowledge gaps and determined that the primary problem with undertaking surveillance of CKD was not due to knowledge gaps. Rather there are critical systems gaps that interfere with successful collection, collation and analysis of what information is available in different data systems. There was general agreement that passive surveillance (utilizing existing data systems) was much more feasible than developing and maintaining active surveillance that requires original data collection required for the surveillance purposes. The passive systems discussed (Table) were:

Mortality: This is the clearest endpoint but the completeness of reporting of deaths and the quality of mortality records are known to vary by country and even within country. One special problem highlighted is the absence of a CKDu category within the ICD/CIE 10 classification. Deaths caused by CKD are coded first under diabetes or hypertension or other conditions such as systemic lupus if these are associated conditions. While there is a sub-series of codes (N18) that can be used to assign CKD stage, this series does not indicate any specific cause. Training on CKD diagnosis and recording should be improved for both physicians and medical record personnel.

Renal Replacement Therapy (RRT) Centers: There are increasing numbers of RRT centers that, using a common format, could provide information to serve as a registry for pre-mortal cases and selected risk factors. Here there is greater opportunity to identify CKDu/CKDnT. However there is no standard reporting or recording forms so collection of case details is likely to be quite cumbersome if comparisons are to be made. Actual RRT registries in Central America are in the very early stages of development or absent.

Hospital or Ambulatory Care Records: These sources could provide much more specific and detailed data about cases of CKD that might permit a better specification of cause and certainly could include more complete information about work. It was suggested, however, that this promise of greater detail about cases recorded by attending physicians is not necessarily so, especially in outpatient care. And there is the added problem of variability in diagnosis as physicians may not be well trained in diagnosis or staging of CKD, especially in earlier stages. It does not appear that any of hospital or outpatient records are in electronic form yet in Central America. This could be anticipated as an area for development as electronic health records find their way into the health care system.

Household or equivalent surveys: These sources have potential to provide a broad population-based understanding of CKD. If well designed, these could account for different causes of CKD and be used to estimate the burden of MeN. Such surveys are labor intense and quite expensive to organize and manage. One example is the Central American Survey of Working Conditions and Health. The first survey did not include sufficiently specific questions to contribute to surveillance of MeN. The 2nd survey, in planning stages, is expected to improve information about hot occupations as well as CKD. This survey is region-wide. Without country-specific surveys it is likely that the information provided will be at a fairly general level.

Occupation or other risk information: As far as is known there is no systematic collection of individual data that can be used to attribute occupation or other types of risk information to individual cases useful for passive surveillance. The obvious advantage of such data would be to examine patterns of CKD by different occupational groups.

Miscellaneous: Mention was made of data systems that might be adapted to surveillance use. Specifically mentioned were i) geographic information systems (GIS) designed to collect, analyze and present all types of spatial or geographical data, and ii) health care or disability payment systems. Either or both of these systems might be linked electronically to health-specific information above to provide new understanding of the patterns of MeN.

Recommendations to move forward (see table)

1. The primary recommendation from the workgroup was to find out what was being done in each country. This will establish a clear baseline of surveillance practices. Emphasis should be placed on the quality and potential for passive surveillance systems since resources are scarce. Lessons learned in each country can be shared so that mistakes are not duplicated and clever methods can be well documented.

The group noted that a range of electronic data systems are likely to be designed in the near future to serve a variety of purposes in the different institutions. As these are developed and adopted in each of the Mesoamerican countries, it is important that a baseline census of systems be available so that components of new electronic systems critical to inform understanding of CKD and MeN can be taken into account. The following should be included in a census of country surveillance capacities:

- Mortality data quality and timely reporting
- Hospital discharge quality and degree of specificity in the diagnoses
- Central RRT centers considering a standard case report format
- Clusters of CKD or MeN identified
- National household and other surveys existing or planned
- Insurance coverage for CKD
- Current resources for surveillance tasks

2. Intensive passive surveillance efforts immediately by selecting the data systems that are most reliable and accurate. These can be expanded and improved upon as resources become available.

3. While active surveillance has many theoretical advantages, these are very resource intensive and expensive. Active surveillance opportunities should be sought, where possible, through add-ons to existing surveys. Keep in mind that surveys beyond those directly related to health may prove helpful (routine household surveys, payment systems, employment systems, disability systems, etc.)

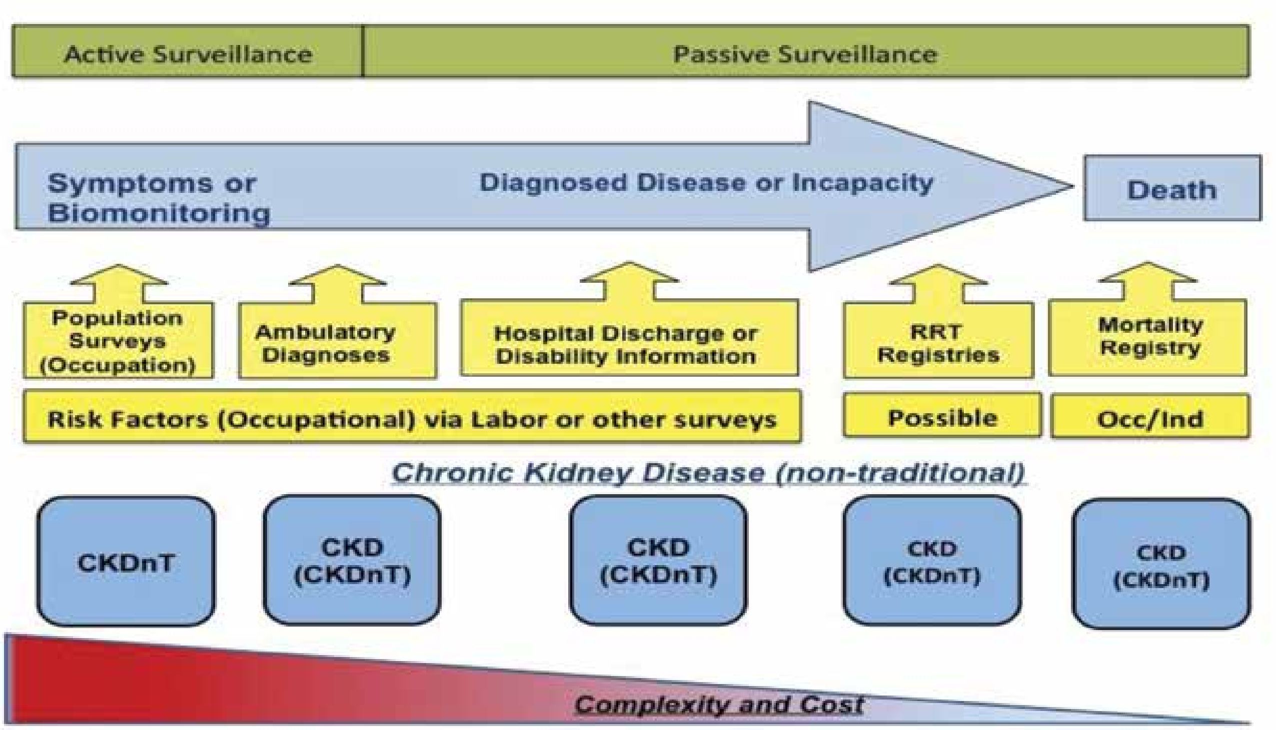
4. Consider innovative use of GIS by taking advantage of environmental and occupational databases that might lend themselves to GIS analysis that targets CKD or CKD risk factors.

5. Examine surveillance “hot spot” signals by an active effort to follow-up these signals to enhance understanding wherever and whenever possible.

Table 1. Summary of relevant issues for CKDu surveillance.

Target	Advantages	Disadvantages	Resource Requirements	Priority	Actions Needed
Mortality	• Clear endpoint • Ease of access • Subnational possible • Basic demographics	• No CKDu/ CKDnT • Incomplete • Quality questions • Limited demographics	Lowest	Highest	• Address disadvantages • Train physicians and medical registry personnel • ICD10 recoding needed
RRT	• Clear endpoint	• Coverage limited • Depending on RRT capacity options for treatment may be limited.	Low	High	• Registry? • CENCAM subcommittee with SLANH could take this forward
Hospital/ Ambulatory care	More complete diagnoses may be available	Variability in diagnosis	Moderate-Intensive	Medium	Establish systems of electronic records
Household or equivalent survey	• Target questions specifically • Nationally representative	Unlikely subnational	Intensive	Low	• Begin discussions • Link to existing surveys
Occupation or other risks information systems	Exposure or job information to link to health system data	Few relevant resources	Low	Medium	Access Ministry of Labor & related sources

Figure 1. Schematic Overview of CKDu Surveillance.



CHRONIC KIDNEY DISEASE IN GUATEMALAN CHILDREN

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and Randall Lou-Meda

Background: Epidemiological information on pediatric chronic kidney disease (CKD) is limited internationally. This study analyzed the registry at Guatemala's only Pediatric Nephrology center. The aim was to describe the distribution of pediatric CKD, estimate incidence and prevalence of pediatric end stage renal disease (ESRD), and estimate time to progress to ESRD.

Methods: Incidence and prevalence were calculated for annual periods. Moran's index for spatial autocorrelation was used to determine significance of geographic distribution of incidence. Time to progress to ESRD and associated risk factors were calculated with multivariate Cox regression.

Results: Of 1545 patient records, 432 patients had CKD. Prevalence and incidence of ESRD were 4.9 and 4.6 per million age related population. Incidence was higher for the Pacific coast and Guatemala City. The cause of CKD was undetermined in forty three percent of patients. . Average time to progress to ESRD was 21.9 months; factors associated with progression were: older age, diagnosis of glomerulopathies, and advanced-stage CKD at consultation.

Conclusions: Prevalence and incidence of ESRD are lower than in other countries. This may reflect poor access to diagnosis. Areas with higher incidence and a large proportion of CKD of undetermined cause are compatible with other studies from the region.

Keywords: Chronic kidney disease, End-stage renal disease, Epidemiology, Risk factors, Pediatric nephrology, FUNDANIER.

COMPREHENSIVE APPROACH TO PEDIATRIC KIDNEY DISEASES IN GUATEMALA

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Abstract: The Foundation for Children with Kidney Disease (FUNDANIER) has been the driving force that has facilitated changes in the Guatemalan health system in order to establish a comprehensive pediatric nephrology program. We previously described the creation and early phases of the FUNDANIER project. This article describes the recent accomplishments of the project with the intention of sharing a model that might be applicable in other developing countries.

Key words: Chronic kidney disease - prevention - kidney foundation - FUNDANIER - pediatric nephrology.

APPLYING QUALITATIVE RESEARCH METHODOLOGY TO CHARACTERIZE YOUNG PATIENTS WITH CHRONIC KIDNEY DISEASE OF UNKNOWN CAUSE IN ARGENTINA. PROJECT DESCRIPTION.

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Introduction: Chronic kidney disease (CKD) is a serious global public health problem. The etiology of this disease has been attributed to "traditional factors", such as diabetes and hypertension, as well as "non-traditional factors", many of which are categorized as CKD of unknown cause. In recent years several publications have reported a high prevalence of CKD of unknown cause in Central American countries, mainly in rural areas affecting men farmers under 60 years, which led the study of its causes by different research groups. In Argentina, data obtained from the National Registry of Dialysis, showed a high prevalence of CKD in Tucuman province compared to the rest of the country, with high frequency of unknown cause. In this province, by 2016, are expected 60 new CKD cases (20 women and 40 men) of unknown cause in the population between 20 and 44. This projection requires further study of these cases deepen their causal knowledge.

Objective: To characterize clinical, environmental and social determinants of the population under 45 years with chronic kidney disease of unknown cause who enter dialysis in the province of Tucuman in Argentina

Methods
Methodological approach: An exploratory study of a case series of patients with chronic kidney disease of unknown cause from qualitative methodology using biographical-narrative research.

Population: People under 45 years with chronic kidney disease

of unknown cause who enter dialysis during 2016 in the province of Tucuman in Argentina.

Data Source: In-depth interviews individually to investigate socio-environmental history of patients.
Analysis: Qualitative materials collected during interviews are liberalized verbatim and process information using content analysis to generate a list of factors and dimensions explanatory power of the health situation of the population and non- traditional risk factors and the relationships postulated among these factors.

Ethical issues: The project will comply with international ethical guidelines written in the Declaration of Helsinki. It shall conform to the legislation of National Law Personal Data Protection No. 25,326 (Law of Habeas Data) to protect the identity, ensuring anonymity and confidentiality of information. For conducting interviews informed consent will be required.

Expected results: To facilitate a systemic understanding of non-traditional risk factors for chronic kidney disease of unknown cause involving the stakeholders themselves in an iterative process for contextual knowledge.

END-STAGE RENAL DISEASE OF UNKNOWN ETIOLOGY IN A SUGARCANE REGION IN ARGENTINA

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Introduction: In the last years, a growing incidence of end-stage renal disease (ESRD) affecting young agricultural workers in several countries has been observed. Unknown etiology (UE) in young people is considered a faulty of preventive measures in controlling risk factors and in surveillance of early damage. In Argentina, dialysis and transplant records are compulsory as the state finances these practices, thus the argentinian public registry has a coverage of more than 95% of ESRD population.

Methods: In this ongoing study we aim to describe the incident rate (IR) of UE-ESRD in men between 20 and 44 years old in the last 10 years comparing a sugarcane main production region (Tucuman) to national IR. Crude and adjusted rates are expressed per million of inhabitants and with 95% confidence Interval. Time trend will be analysed using joint point.

Preliminary results: For year 2013, ESRD total adjusted IR for Tucuman was 225 (CI 95% 201-252) vs 160 (CI 95% 156-164) for national rate (p 0.001). In Tucuman, ESRD crude rate for women was 167 (vs overall 128) and 237 for men (vs overall 193). The UE is 17% of the total incidental cases, and it appears to be the main etiology among younger people (20 to 44 years old). The national UE-ESRD rate for 2011-2013 was 25 while for Tucuman it was 31.4 being Tucuman the second largest province in crude incidence. This study is in process to calculate UE and other etiologies adjusted rate by age and sex and regions for Argentina.

Conclusion: The preliminary results show that sugarcane region in Argentina is one of the higher region of UE in incident dialysis patients. Final results will help us understand if in some region of Argentina there also exists an epidemic of UE-ESRD in young people.

PREVALENCE OF TRADITIONAL AND NON TRADITIONAL RISK FACTORS OF CHRONIC KIDNEY DISEASE IN ROOSEVELT HOSPITAL, GUATEMALA

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Introduction: Chronic Kidney Disease (CKD) is considered by the World Health Organization (WHO) as a worldwide epidemic. The traditional causes of CKD are diabetes mellitus (DM) (40%) and hypertension (HT) (30%). In Central America, in the last 20 years it has been reported an increase in CKD prevalence not associated with traditional causes (CKDnT). CKDnT has been reported in young men and farmers in several communities of southern Nicaragua and El Salvador. Possible causes of CKDnT include exposure to pesticides, heat-induced stress, indiscriminate use of nonsteroidal anti-inflammatory drugs (NSAIDs) and infections. At Roosevelt Hospital, the largest referral hospital in Guatemala, CKD is the leading cause of hospitalization. However, it is yet unknown the characteristics of CKD patients and the prevalence of CKDnT.

Objectives: To determine the prevalence of traditional CKD risk factors and CKDnT in Roosevelt Hospital in Guatemala.

Methods: Cross-sectional study at Roosevelt Hospital in Guatemala City. All CKD patients were interviewed, regardless of time since diagnosis. Patients over 12 years and of both sexes were included. We used a previously validated suvery that includes 83 questions evaluating demographic and occupational factors, and traditional and non-traditional CKD risk factors. Diabetes and hypertension were considered as traditional risk factors. Non-traditional risk factors include occupation and time of the workday and hydration during the day, use of NSAIDs and antibiotics, birth weight, home remedies, and the source of water for consumption.

Results: We interviewed 249 patients, 128 (51%) were male. The age range was 12-84 years old. The average age by sex was 48±17.91 male and 46±19.36 female. Fifty-four percent were from Guatemala City, followed by the southern state of Escuintla (20%). Consequently, most of the patients live in a mild weather

and over 1000 meters above sea level. Less than half (103, 41%) are newcomers and the rest already had a previous diagnosis ($p=0.004$). Among those who had traditional risk factors 170 (68%) were hypertensive and 103 (41%) diabetics ($p<0.001$). One-quarter (61) patients had no traditional risk factors. Four (1.5%) were excluded due to co-morbidities that lead to the CKD. Of the 57 patients without traditional risk factors or co-morbidities, they were, on average, significantly younger compared to those with traditional risk factors (35±18.5 years vrs. 50±17.3 years old, $p<0.001$). The frequency of use of NSAIDs and home remedies was significantly ($p<0.05$) higher among those with non-traditional risk factors compared to their counterparts with traditional ones. The percentage of patients working in agriculture was not different between those with non-traditional and traditional risk factors (33% and 37%, respectively). Corn cultivation was the most frequently reported activity in both groups and most had contact with pesticides. Working hours in the no-traditional risk factor group were between 8 and 16 hours and water consumption during working hours was 2 to 5 liters (not significantly different from those with traditional risk factors). The largest source of water of all CKD patients is well, pipeline and river.

Conclusion: In the largest public referral hospital in Guatemala, one quarter of the patients lack traditional CKD risk factors. Of the proposed possible risk factors, we did not find any higher prevalence in those with no traditional risk factors compared to those with traditional ones. The possible etiology of CKDnT deserves further research before the diagnosis of CKD is made.

Keywords: Chronic Kidney Disease, Occupational Disease, Epidemiology, Central America.

EXPOSURE TO NEPHROTOXIC POLLUTANTS IN LAS BRISAS COMMUNITY, EL SALVADOR

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Introduction: In the former formulator pesticide factory AGROJELL S.A. de C.V., located in the municipality of San Miguel of El Salvador, 92 barrels of toxaphene, an obsolete pesticide with nephrotoxic properties, were improperly stored since early 90s until 2010. San Miguel is a city located close Chaparrastique volcano and west of Río Grande de San Miguel one of the major rivers of the country. Around the former factory there are Las Brisas communities where some families are supplied by shallow wells, some of them with presence of toxaphene according analysis carried out in 2011 by the Ministry of Enviroment. Las Brisas community has a high prevalence of Chronic Kidney Disease nontraditional causes (CKDnt), a disease whose main risk factors are related to work conditions of agricultural workers and to exposure to toxics as pesticides and heavy metals. We examined the presence of common nephrotoxic pollutants in water in El Salvador as arsenic (volcanic materials and hydrothermal water are important sources of arsenic in El Salvador) and paraquat (the most widely used pesticide in El Salvador).

Methods: Waters from community wells (groundwater) and surrounding rivers (surface water) were sampled during dry season in 2014. Physicochemical water parameters were obtained in situ and chemical analysis to identify, arsenic (Graphite furnace atomic absorption) and paraquat (Spectrophotometer UV-VIS) were carried out by the National Reference Laboratory of Ministry of Health of El Salvador.

Results: According the sampling analysis carried out in this study, surface and groundwaters of Las Brisas communities can be described as hard and very hard waters (136-419 mg/L) with Arsenic content reaching maximum values of 0.01 mg/L (0.01 is the standard proposed by Salvadoran Consumption Water Quality Guidelines) and with some wells with paraquat pollution reaching maximum values of 1.69 mg/L (0.62 mg/L is the standard proposed by Salvadoran Consumption Water Quality Guidelines).

Conclusion Through water intake form domestic wells, Las Brisas population has been exposed to a nephrotoxic load formed mainly by toxaphene, arsenic and paraquat. This chronic exposure could explain the high prevalence of CKDnt of Las Brisas community, whose inhabitants, in general, are not related to agriculture. Identified high hardness of water in serving wells also could be considered as risk factor of CKDnt according recent hypothesis proposed by Sri Lanka researchers.

Keywords: CKD of nontraditional causes, Obsolete pesticides, Arsenic, Toxaphene, Paraquat, Water hardness, El Salvador.

WEATHER TRENDS AT A SUGAR MILL IN NORTHWEST NICARAGUA, 1973-2013

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Background: Over the past two decades an epidemic of chronic kidney disease of non-traditional etiology (CKDnT), also termed Mesoamerican Nephropathy (MeN), has been identified as a public health emergency in Central America. Sugar cane workers are among the most affected populations. Although the causes of MeN remain unknown, heat stress, a growing concern in a warming climate, has been identified as one potential cause, or an effect modifier of other nephrotoxic exposures, including agrichemicals, heavy metals and infectious agents.
We analyzed weather conditions over four decades in a region of high incidence of CKDnT to assess average changes in annual temperature, changes in temperature variability, and related climate data.

Methods: We used daily weather data collected from 1973 to 2013 at a weather station located at sugar mill of the region of Chinandega, in northwest Nicaragua (at the epicenter of MeN epidemic), including minimum, average, and maximum temperature (°C); minimum, average, and maximum relative humidity (%); hours of sunlight per day; wind speed (km/24 hours); evaporation (inches); and precipitation (inches). We used extreme weather indicators based both on daily absolute mean values, percentile based values and threshold indicators, developed by the World Climate Research Programme's Expert Team on Climate Change Detection and Indices. We fit linear regression models for each extreme weather variable as a function of calendar year, and calculated

decadal trends as changes per decade based on above derived regression coefficients.

Results: Preliminary results show that in each decade the annual average maximum temperature increased 0.26 °C ($p=0.04$) and the average maximum temperature during the dry season (November to April approx.) increased 0.30 °C ($p=0.01$). It also increased by a quarter of a degree in April, the hottest month of the year. The minimum temperature in a given year decreased per decade 0.46 °C ($p=0.005$) both on an annual and dry season basis. We found a statistically significant increased standard deviation of daily mean temperatures both on an annual and dry season basis, an indicator of long-term temperature variability, which results in hotter days and/or cooler nights. Analyses are ongoing.

Conclusion: We found evidence that both average maximum and long-term variability of temperatures has increased over the past three decades. This is particularly important during dry seasons (when the harvest occurs). These changes can be a potential burden for workers' capability to adapt to climate conditions. If heat stress does play a key role in the MeN epidemic as hypothesized, the at-risk population will continue to grow with predicted increases in both temperature and frequency and intensity of heat waves due to climate change. Furthermore, climate models have shown that tropical, low-latitude regions display the earliest significant warming, and are also the most vulnerable due to low adaptive capacity.

END-STAGE RENAL DISEASE INCIDENCE, MORTALITY, AND PREVALENCE IN A HOT SPOT OF MESOAMERICAN NEPHROPATHY IN EL SALVADOR: A TEN-YEAR COMMUNITY REGISTRY

Ramón García-Trabanino[1,2] MD, Carolina Hernández[2,3] MD, Adrián Rosa[2,4] MD, Jesús Domínguez Alonso[2,5] MD. On behalf of the Emergency Social Fund for Health of Tierra Blanca, Usulután, El Salvador. [1]Association of Nephrology and Hypertension of El Salvador, San Salvador, El Salvador. [2]Emergency Social Fund for Health of Tierra Blanca, Usulután, El Salvador. [3]Integral Health Basic System (SIBASI) Usulután, Ministry of Health, Usulután, El Salvador. [4]Medic Unit Puerto El El Triunfo, Salvadoran Institute of Social Security (ISSS), Usulután, El Salvador. [5]Primary care, Northwest Jaén sanitary area, Andalucía, Spain.

Abstract: The Bajo Lempa is an impoverished, rural coastal region of El Salvador affected by a chronic kidney disease epidemic named the Mesoamerican nephropathy. The emergency social fund for health (ESFH), a local communal organization, helps to fight the epidemic in 42 communities (N=19223; mean age 26,7 years; 51,5% female, 48,5% male; 40,2% <18 years) of the region.

Aims: To report annual rates of end-stage renal disease (ESRD) incidence and patient mortality in these communities during a 10 year period (2004-2013), and the prevalence of patients receiving renal replacement therapy (RRT) at year 2013.

Methods: The ESFH registered new ESRD cases, their basic past history, RRT modality if received, and their deaths.

Results: In 10 years we registered 271 new cases (annual average 27,1; 11% female, 89% male; mean age 55,6 years, four <18 years). Average annual ESRD incidence rate: 1409,8 per million population (pmp). Ninety-four patients received RRT (34,7%): 58 in the Ministry of health, 9 in the social security, 1 in the military health, and 26 in private services. Two hundred forty-six patients died (annual average 24,6; 10,6% female, 89,4% male; mean age 56,1 years; 92,3% at their home). Average annual mortality rate: 128/100000 population. Prevalence of patients receiving RRT at year 2013: 1300.5 pmp (N=25; 16% female, 84% male; mean age 51 years).

Conclusions: This region has a high incidence of ESRD. Few receive RRT. Patient mortality is high with or without RRT. Most are male (9:1). Social determinants influence the high mortality.

NATIONAL PREVALENCE OF END-STAGE RENAL DISEASE PATIENTS UNDER RENAL REPLACEMENT THERAPY IN EL SALVADOR, YEAR 2014

Ramón García-Trabanino[1,2], Zulma Trujillo[3], Ana Verónica Colorado[4], Salvador Magaña Mercado[5] y Carlos Atilio Henríquez[6]. On behalf of the association of nephrology and hypertension of El Salvador (ANAHES).

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Abstract: With 21041 km² and 6401240 inhabitants for 2014, El Salvador suffers the epidemic called Mesoamerican nephropathy (MeN) and has the highest renal failure mortality rate of the Americas. Five healthcare providers offer renal replacement therapy (RRT). The exact national RRT prevalence has never been reported. Aims: report RRT prevalence during the third trimester 2014, and patients' basic characteristics. Methods: The association of nephrology coordinated a standardized instrument, registering patients in all 31 RRT centres from all healthcare providers nationwide. Results: during 2014, 3807 patients were undergoing RRT, mean age 50.42 years old, 67.5% male. Etiology of end-stage renal disease was: not reported or undetermined 50%, hypertension 21.1%, diabetes 18.9%, glomerulonephritis 6.7%, obstructive causes 1.2%, tubulointerstitial 0.9%, polycystic 0.4%, congenital and others 0.7%. Social security is the main RRT provider attending 49.7% of patients. National prevalence 2014 was: total RRT 595 per million population (pmp), peritoneal dialysis (PD) 289 pmp, haemodialysis 233 pmp, kidney transplantation 74 pmp (living donor only). Generally, coastal and lowlands municipalities showed higher prevalence. Only 4.8% haemodialysis patients receive it thrice weekly. Only 40.9% PD patients belong to a continuous ambulatory or automatized program, and 25.4% still use rigid catheter. Discussion: Despite the significant increase in RRT services in recent years the national RRT prevalence is still insufficient, lower than the Latin American average (660 pmp). Three fourths of haemodialysis and PD patients are infradialyzed. Old RRT techniques are still used. RRT patients are younger than expected and male gender predominates, matching the epidemiological pattern of MeN.

HEAT EXPOSURE, VOLUME DEPLETION AND ACUTE KIDNEY INJURY IN CALIFORNIA'S AGRICULTURAL WORKERS

Moyce, S., Joseph, J. Tancredi, D., Mitchell, D., Armitage, T. Schenker, M.
University of California, Davis

Objective: Chronic kidney disease in Central America suggests agricultural work is potentially harmful to the kidneys. We investigated the cumulative incidence of acute kidney injury (AKI) over one work shift agricultural workers in California and estimated associations of heat exposure and volume depletion on incident AKI.

Methods: Serum creatinine measurements were collected both before and after a work shift to estimate AKI. Heat exposure was estimated via the physiologic strain index using core body temperature and heart rate measurements. Volume depletion was estimated via change in body mass after a work shift. Associations of incident AKI with heat exposure and volume depletion were tested using logistic regression.

Results: In 295 agricultural workers, AKI after a work shift was detected in 35 participants (11.8%). Preliminary analyses show weight loss to be associated with twice the odds of incident AKI (adjusted odds ratio 2.11, 95% confidence interval 1.15-3.90). (Heat exposure results pending, but will be presented in final poster.)

Conclusions: The cumulative incidence of AKI after a single day of agricultural work is alarming due to increased risk of long-term kidney damage and mortality. The association with volume depletion suggests AKI may be prevented with proper rehydration during a work shift. These results also indicate AKI in California's workers may be linked to Mesoamerican Nephropathy.

CUMULATIVE INCIDENCE OF ACUTE KIDNEY INJURY IN CALIFORNIA'S AGRICULTURAL WORKERS

Sally Moyce, Jill Joseph, Daniel Tancredi, Diane Mitchell, Marc Schenker
University of California, Davis.

Objective: Chronic kidney disease in Central America suggests agricultural work is potentially harmful to the kidneys. We investigated the cumulative incidence of acute kidney injury (AKI) over one work shift among agricultural workers in California.

Methods: Serum creatinine was measured both before and after a work shift to estimate AKI. Associations of incident AKI with traditional and occupational risk factors were tested using chi-square and trend tests and logistic regression.

Results: In 295 agricultural workers, AKI after a summer work shift was detected in 35 participants (11.8%). Piece-rate work was associated with 4.52 adjusted odds of AKI (95% confidence interval 1.61-12.70).

Conclusions: The cumulative incidence of AKI after a single day of summer agricultural work is alarming due to increased risk of long-term kidney damage and mortality.

Moyce, S., Joseph, J., Tancredi, D., Mitchell, D., & Schenker, M. (2016). Cumulative Incidence of Acute Kidney Injury in California's Agricultural Workers. Journal of Occupational and Environmental Medicine, 58(4), 391-397.

URINARY BIOMARKERS KIM-1 AND NGAL FOR EARLY PREDICTION OF CHRONIC INTERSTITIAL NEPHRITIS IN AGRICULTURAL COMMUNITIES IN SRI LANKA.

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High incidence of Chronic Interstitial Nephritis in Agricultural Communities (CINAC) is reported in rural Sri Lanka. Victims do not exhibit common causative factors such as hypertension, diabetes or glomerulonephritis. Previous studies have identified agricultural activities (usage of herbicides and phosphate fertilizers), repeated dehydration, and genetic susceptibility as potential risk factors. Although CINAC is a tubular disease, urine albumin or albumin-creatinine ratio is still being used as the screening tool.

Proximal tubular epithelial cells express Kidney Injury Molecule (KIM-1) and Neutrophil Gelatinase-Associated Lipocalin (NGAL) in response to renal injury. KIM-1 and NGAL are considered urinary biomarkers for early prediction of tubular injuries. Nevertheless, they have not been used for early perdition of CINAC in Sri Lanka. In present study, we report the use of non-invasive, rapid and sensitive marker of tubule-epithelial cell damage (KIM-1 & NGAL) for early CINAC diagnosis in Sri Lanka.

For determination of KIM-1 and NGAL levels, urine and blood samples were collected from non endemic controls living in wet zone (Matara-M) and in two study locations representing farming communities located in dry zone (i.e. Angunakolapelessa □ (H-A) and Bandagiriya □ (H-B). Urine creatinine and serum creatinine were measured using Jaffe rate-blanked creatinine assay and eGFR was calculated using both CKD-EPI and MDRD equation. Urinary KIM-1 and NGAL levels were measured using specific KIM-1 (Cusabio, P.R. China) and NGAL (Ray Biotech, USA) Enzyme Linked Immuno Sorbent Assay (ELISA) kits. H-A and H-B subjects were further subdivided into two groups depending on their albumin-creatinine ratio (ACR) and serum creatinine levels. Subjects with ACR $\geq$ 30 mg/g and serum creatinine level > 1.3 mg/dl was considered as CINAC patients after excluding other risk factors and the rest were considered as endemic controls.

In M group (N=27) CINAC was not reported. Creatinine adjusted urinary KIM-1 (μg/g Cr) and NGAL (ng/mg Cr) concentrations in M group were (2.885 ± 0.524, Mean ± SEM; Min=0.208; Max= 8.943) and (0.568 ± 0.108 Mean ± SEM; Min=0.024; Max=2.234) respectively.

Creatinine adjusted urinary KIM-1 (μg/g Cr) concentrations in H-A endemic control group (16.852 ± 4.766, Mean ± SEM; Min= 0; Max= 73.391; N= 20; $p<0.05$) were 5 times higher than the non-endemic controls. However, NGAL concentrations in H-A endemic control group (0.797 ± 0.161 Mean ± SEM; Min= 0; Max= 2.499; N=20; $p>0.05$) were not significantly different from the non-endemic control group. When compared to the control groups (M and H-A) creatinine adjusted urinary KIM-1 (μg/g Cr) and NGAL (ng/mg Cr) concentrations were significantly higher in H-A CINAC group (60.165 ± 11.414 Mean ± SEM; Min= 2.552; Max= 176.113; N=15, $p<0.05$) and (2.310 ± 0.586 Mean ± SEM; Min=0.136; Max= 8.785; N=15, $p<0.05$).

Urinary KIM-1 and NGAL concentrations in H-B endemic control group were (10.507 ± 2.477 Mean ± SEM; Min=0; Max= 42.903; N=26) and (1.158 ± 0.14 Mean ± SEM; Min= 0.179; Max= 2.78; N=26) respectively. Urinary KIM-1 concentrations in H-B CINAC group (43.881 ± 9.589 Mean ± SEM; Min= 1.961; Max= 87.476; N=10; $p<0.05$) were 15 times higher than the non-endemic M control group whereas Urinary NGAL concentrations (6.297 ± 2.284 Mean ± SEM; Min= 0.394; Max= 24.123; N=10; $p<0.05$) were 11 times higher than non-endemic M control group. Urinary KIM-1 and NGAL concentrations were also significantly higher in CINAC cases in H-B with compared to the control groups ($p<0.05$) indicating that urinary KIM-1 and NGAL concentrations may be used as early predictive biomarkers for CINAC patients in Sri Lanka.

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RO WATER PLANTS: A SUCCESSFUL SHORT-TERM SOLUTION FOR CINAC IN SRI LANKA

Sarath Gunatilake, Channa Jayasumana and Sisira Siribaddana

Chronic interstitial nephritis in agricultural communities (CINAC) is a rapidly progressing health issue in the dry zone of the Sri Lanka. Synergistic chemical nephrotoxicity caused by glyphosate, paraquat, herbicide surfactants and heavy metals, heat stress and chronic repeated dehydration are hypothesized as main etiological factors of the disease. It is very likely that a combination of these factors is involved in the pathogenesis of the disease, rather than a single factor acting alone. CINAC is an irreversible disease. Therefore, identifying the risk factors and implementing all of known strategies to slow down the progression of the epidemic is mandatory.

One of the main preventive strategies pushed by us was social and political measure to guarantee nephrotoxin free drinking water and ensure adequate hydration. Providing adequate clean water addresses both possible etiologies.

Large man-made reservoirs were the main sources of drinking and irrigation water in the dry zone, Sri Lanka. These reservoirs belong to cascade irrigation system and was initially built during the time of ancient kingdoms (3BC-12 AC) and renovated during the last century. However, with the introduction of chemical farming in 1960s and 70s, it was commonly believed that the reservoir water is contaminated with agrochemicals including the pesticides and the triple phosphate fertilizer. This situation prompted many farming families to use shallow wells as the main source of drinking water. However, when the monsoonal rains flooded the terrain of these shallow wells year after year these wells became contaminated with agrochemicals as well. The water became increasingly hard and distasteful. This could have led to a reduction in the water intake as well. Later analysis of this well water at the California State University, Long Beach labs showed the presence of agrochemical residues.

Although we do not have data to compare water intake prior to the 1960s and now, there is anecdotal evidence to show that it was reduced mainly due to distaste resulting from high Ca, Mg and F levels. Hence, it was imperative to introduce a strategy to purify and enhance the quality of ground water in order to regularize the amount of water consumed by farmers. The solution was Reverse Osmosis technology. Reverse Osmosis, commonly referred to as RO, is a process of demineralizing or deionizing water by pushing it under pressure through a semi-permeable RO membrane which allows the passage of water molecules but not the majority of inorganic ions, organic molecules, bacteria and pyrogens.

Although maintaining RO machine in rural settings is an enormous challenge, more than 25 large scale machines (> 10000 L/day, cost- $ 20000), 250 middle scale machines (500-10000 L/day, cost-$ 2000) and 25000 domestic machines (100 L/day, cost- $ 300) have been established in CINAC endemic regions for the last 5 years. The majority of large and middle scale plants were funded by government and private donors and established through community-based organizations. Domestic machines are self-funded. Our experience up to now has shown that this may be a viable temporary measure in dealing with drinking water supply issues in CINAC affected areas.

HEAT STRESS EXPOSURES ON KIDNEY DYSFUNCTION – AN EXPLORATORY STUDY IN A STEEL INDUSTRY.

Vidhya Venugopal, Rekha. S, Latha. P.K.,Manikandan.K. Department of Environmental Health Engineering, Sri Ramachandra University, Chennai, India.

Background & Purpose: Raised temperatures and shifting humidity conditions due to Climate Change are likely to increase the heat stress for workers in physically exerting and high heat occupations like in steel manufacturing, with potential risks of adverse kidney function. We have conducted an exploratory study in a steel manufacturing in Southern India to test this hypothesis.

Methodology - We conducted a cross-sectional study with 342 steel workers working in high heat environments engaged in heavy labor for more than 5 years in the industry. Area WBGTs (n=218) were assessed to evaluate the heat exposures and physiological parameters like Core body temperature (CBT), Sweat Rates (SwR) & Urine specific gravity (USG) were assessed as indicators of heat strain. Ultra sound of kidney was conducted in a subset of participants (n=91) based on clinical history and symptoms.

Findings - Workplace heat exposures exceeded the threshold limit value for safe manual work in 156 locations (Avg.WBGT of 33.4°C±3.76°C). Increase in CBT above 1°C in about 14% of the workers (n=48) and SwRs higher than 1.0 L/hr in 15% of workers was recorded. USGs >1.02 in 8.8% of the workers indicated moderate dehydration. Of the 91 workers with a clinical history of reported symptoms of burning sensation, hesitant urination & pain in loins and flanks, 39 workers were positive for some kidney anomaly in Ultrasound of Kidney. 70% of these workers were employed in high heat zones like in furnace areas with high exposures to heat over 5 years.

Conclusion: The preliminary results of this study points at heat stress, heavy manual workload and chronic dehydration as the major risk factors for the disease development in the study population. Periodic surveillance using urinary biomarkers and enhancing welfare facilities for the workers are imperative to avert adverse health consequences as climate change proceeds.

Keywords: Sweat rate, heat stress, urine specific gravity, kidney dysfunction.

PESTICIDE EXPOSURE AND CHRONIC KIDNEY DISEASE

Jill Lebov, Research Epidemiologist, RTI International, Research Triangle Park, NC

Experimental studies suggest a relationship between pesticide exposure and renal impairment, but epidemiological research on the long-term effects of chronic low-level and short-term high-level pesticide exposure on renal disease risk is limited. The poster provides a brief outline of the existing evidence for a relationship between pesticide exposure and kidney disease, including results from a population-based study in Nicaragua, in which we observed a higher prevalence of chronic kidney disease with increasing years of work in agriculture. This poster also describes findings from a recent study of pesticide applicators in the United States, in which elevated risk of end-stage renal disease (ESRD) was associated with long-term use of the herbicides alachlor, atrazine, metolachlor, paraquat, and pendimethalin, and the insecticide permethrin. Additionally, more than one medical visit due to pesticide use (hazard ratio (HR)=2.13; 95%CI 1.17-3.89) and hospitalization due to pesticide use (HR=3.05; 95% CI 1.67–5.58) were significantly associated with ESRD. Our findings support a possible association between ESRD risk and chronic exposure to certain pesticides and suggest that pesticide exposures requiring medical attention may increase the risk of ESRD.

The workshop was organized by SALTRA in collaboration with the CENCAM Board and the MeN 2015 Organizing Committee. It was made possible thanks to the dedication of many individuals, including those who participated. We extend our most profound thanks to the following individuals who dedicated their time and talents:

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- Pan American Health Organization (PAHO)
- The International Society of Nephrology (ISN)

All other participants either paid their own way or obtained external funding to attend. We know many participants went to great lengths to be able to attend, and that this is a reflection of their willingness to work toward finding the causes of and solutions for MeN.

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2ND INTERNATIONAL WORKSHOP ON MESOAMERICAN NEPHROPATHY

November 18-20, 2015

Workshop Objectives

Chronic Kidney Disease of non-traditional causes is a public health problem of such a magnitude and severity in Mesoamerica that the Central American Council of Ministries of Health recently called for urgent action. MeN 2015 is a response to this call for action and will result in the most exhaustive and up-do-date review of the science, elucidating the potential causes of the epidemic, research recommendations, as well as possible solutions for prevention and mitigation. The workshop has a number of ambitious aims. These are:

1. **Update progress in understanding the epidemic and on the research questions identified at First International Workshop.**
2. **Share ongoing studies in the region and identify current knowledge gaps.**
3. **Articulate key hypotheses and strength of evidence to date with a view to focus future research on the most promising hypotheses.**
4. **Promote and establish new relationships and collaboration among researchers and clinicians.**
5. **Identify data and data sources to inform the public, clinicians, labor market partners, and policy makers in understanding the evidence base of interventions and solutions for the prevention and treatment of CKDnT.**
6. **Strengthen the communication and support structure for researchers in the region.**
7. **Publish proceedings, peer-review papers summarizing progress and research gaps and host in-person CENCAM meeting.**

The Workshop brings together researchers from around the world who are working on the epidemic to share knowledge, techniques, data and hypotheses and plans to translate research into practice.

More information about CENCAM is available here: http://www.regionalnephropathy.org/?page_id=141

Wednesday, 18 November	
08:00-9:00	Registration
09:00-10:00	Inauguration
10:00-10:15	Coffee Break
Theme: What do we know?	
10:15-12:15	**Advances in Knowledge of CKDnT** **Chair:** Daniel Brooks, Boston University, USA
	• **What has happened since the 1st Mesoamerican Nephropathy Workshop?** Catharina Wesseling, Chair CENCAM, Karolinska Institutet, Sweden
	• **In which countries and occupations has CKDnT been reported in excess and how well has it been studied where there are no reports?** Agnes Soares da Silva, PAHO/WHO, Washington DC Kristina Jakobsson, Gothenburg University, Sweden
	• **CKD in Sri Lanka** Channa Jayasumana, Rajarata University, Sri Lanka
	• **Government and health care systems response in Central America** Julietta Rodríguez-Guzmán, PAHO/WHO, Washington DC
	• **Moderated Discussion**
12:15-13:30	**Lunch**
13:30-15:30	**Reviews of Evidence for CKDnT in Relation to Hypotheses**
	Chair: Kristina Jakobsson, Gothenburg University, Sweden
	• **Heat and dehydration** Daniel Brooks, Boston University USA Jennifer Crowe, Universidad Nacional, Costa Rica Rebekah Lucas, University of Birmingham, UK

	• **Does exposure to toxic metals have a role in the development of Mesoamerican Nephropathy (MeN)?** Carl-Gustav Elinder, Karolinska Institutet, Sweden Channa Jayasumana, Rajarata University, Sri Lanka
	• **Chronic kidney disease of undetermined etiology and pesticide exposure: an update on recent data** Mathieu Valcke, National Institute of Public Health, Canada Carlos Orantes, Instituto Nacional de Salud Pública, El Salvador
	• **Proposed mechanisms for chronic kidney disease of uncertain etiology observed in Central America (Mesoamerican Nephropathy)** Richard J. Johnson, University of Colorado, USA Ramón García-Trabanino, Assoc. of Nephrology and Hypertension of El Salvador
	Moderated Discussion
15:30-16:00	**Coffee Break**
16:00-17:30	**Experiences from Ongoing Studies** **Chair**: Catharina Wesseling, Chair CENCAM, Karolinska Institutet, Sweden
	• **WE program pilot intervention 2014-2015: Lessons learned** Theo Bodin, Karolinska Institutet, Sweden Ramón García-Trabanino, Assoc. of Nephrology and Hypertension of El Salvador David H. Wegman, University of Massachusetts Lowell, USA
	• **Boston University School of Public Health: Studies of Occupational and Non-Occupational Risk Factors for Chronic Kidney Disease** Michael McClean, Boston University, USA David Friedman, Boston University, USA
	• **Gaining insights into the evolution of CKDnt from community-based follow up studies** Ben Caplin, London School of Hygiene and Tropical Medicine, UK Neil Pearce, London School of Hygiene and Tropical Medicine, UK Marvin González, National Autonomous Univ. of Nicaragua at León (UNAN-León)
	• **Moderated Discussion**

Programa Financiado por la Unión Europea

17:30-18:00	• **Summary of the Day** Carolina Guzmán Quilo, San Carlos University Guatemala Madeleine Scammell, Boston University, USA

Thursday, 19 November

08:00-8:30	**Announcements and Explanation of the Day´s Activities**
08:30-09:30	• **Clinical Conditions and Pathology** **Chair:** Ramón García-Trabanino, Association of Nephrology and Hypertension of El Salvador
	• **What is known about the Burden and Clinical Characteristics of Mesoamerican Nephropathy?** Ricardo Correa Rotter, National Medical Science and Nutrition Institute, Mexico Zulma Cruz de Trujillo, Hospital Nacional Rosales, El Salvador
	• **Pathology and pathophysiology of Mesoamerican nephropathy and comparisons with hypertension/diabetes CKD and CKDnT outside Mesoamerica** Annika Östman Wernerson, Karolinska Institutet, Sweden Julia Wijkström, Karolinska Institutet, Sweden
	• **Moderated Discussion**
9:30-9:45	**Coffee Break**

Theme: What do we need to know and understand?

9:45- 11:15	**Working Groups (A) - Next Steps to Address Knowledge Gaps** *At registration, each participant will be asked, to prioritize (highest 5) the eleven Working Groups that are of most interest. The Organizing Committee will use these priorities to assign participants to one Working Group (A) and a different Working Group (B) to balance participant interests and number of participants in each group.*

1. Exploring biomarkers for early evidence of abnormal kidney function

a. Objectives: Discuss strengths and limitations of biomarkers, the time course of their appearance in non-diseased populations and the priority of single or combinations of biomarkers to serve as study endpoints in field and laboratory studies.

b. Output: The best possible consensus of which biomarkers should be considered priority.

- **i.** Group Leaders: Carl-Gustaf Elinder, Karolinska Institutet, Sweden; Ricardo Correa Rotter, National Medical Science and Nutrition Institute, Mexico.
- **ii.** Rapporteur: James Kaufman, Boston University, USA.

2. Exploring genetic and epigenetic susceptibility

a. Objectives: Discuss evidence for susceptibility, measurement of genetic or epigenetic markers, potential for use in field and laboratory studies.

b. Output: Propose markers of susceptibility that might be appropriate to use in field studies whenever possible and/or markers that should be a priority focus for laboratory investigation.

- **i. Group Leader:** David Friedman, Harvard University, USA
- **ii. Rapporteur:** Joseph Kupferman, Beth Israel Deaconess Hospital, Boston, USA

3. Assessing individual risk factors

a. Objectives: Discuss evidence for importance of factors such as NSAIDs, nutrition, alcohol and exposure, the potential for estimating exposure levels and approaches to assuring validity of measures in the field and in an experimental setting

b. Output: The best possible consensus of which factors are most important to consider in field studies

- **i. Group Leader:** Aurora Aragón, UNAN-León, Nicaragua
- **ii. Rapporteur:** Manuel Cerdas, Mexico Hospital, San Jose, Costa Rica

4. Assessing exposures to pesticides and metals

a. Objectives: Consider the evidence for exposure to pesticides and to metals to explain epidemics of CKDnT, the best methods to measure and quantify these for use in population and experimental studies and how to assure validity of measures in the field and in an experimental setting

b. Output: Identify which pesticides and which metals are a priority for consideration in studies of CKDnT and how to quantify exposures.

- **i. Group Leader:** Kristina Jakobsson, Gothenburg University, Sweden
- **ii. Rapporteur:** Berna van Wendel de Joode, Universidad Nacional, Costa Rica

	5. Assessing exposure to environmental heat load/dehydration and workload **a. Objectives:** Consider the essentials of field assessment and quantification of heat load/dehydration and workload in both short and long-term studies and how to assure validity of measures in the field and in an experimental setting **b. Output:** Propose priority measures of heat/dehydration and of workload that are necessary to include in population studies or to examine in laboratory investigations **i. Group Leaders:** Rebekah Lucas, University of Birmingham, UK; Esteban Arias Monge, Costa Rican Technol. Institute, Costa Rica **ii. Rapporteur:** Jennifer Crowe, Universidad Nacional, Costa Rica
	6. Consideration of infectious agents **a. Objectives:** Consider evidence for infectious (bacterial, parasitic or viral) etiologies for CKDnT and how these might be assessed in field studies **b. Output:** Propose which, if any, infectious agents are important to further assess in population or laboratory studies of CKDnT **i. Group Leader:** Reina Turcios-Ruiz, CDC, Atlanta, USA **ii. Rapporteur:** Juan José Amador Velázquez, Boston University, USA

Thursday, 19 November (continued)

	7. Understanding the mechanism of MeN – Theory **a. Objectives:** Examine proposed mechanisms for etiology of MeN and CKDnT and consider both epidemiologic and laboratory evidence in support of these **b. Output:** Characterize the most promising hypotheses and propose laboratory and/or field studies to confirm or refute **i. Group Leaders:** Rick Johnson University of Colorado, USA; Annika Östman Wernerson, Karolinska Institutet, Sweden **ii. Rapporteur:** Catharina Wesseling, Chair CENCAM, Karolinska Institutet, **ii.** Sweden

	8. Developing central elements for a Core Questionnaire **a. Objectives:** Enhance comparison of study findings across different populations, prioritize common core questions that could be agreed on to include in future studies **b. Output:** Propose a core questionnaire using questions from already standardized instruments (if available) and questions that need validation for use studying MeN **i. Group Leader:** Daniel Brooks, Boston University, USA **ii. Rapporteur:** Marvin González, National Autonomous Univ. of Nicaragua at León (UNAN-León)
	9. Approaches to intervention **a. Objectives:** Discuss approaches to intervention in light of current knowledge, discuss those that warrant immediate action and propose feasible study designs to assess their value in preventing MeN **b. Output** – Propose interventions that should be implemented now and how best to assess efficacy and effectiveness in the short and long-term. **i. Group Leader:** Theo Bodin, Karolinska Institutet, Sweden **ii. Rapporteur:** Ilana Weiss, La Isla Foundation, Nicaragua
	10. Understanding macro factors **a. Objectives:** Since the epidemic(s) exists in a social context how can we study the context with respect to socio-economic status, migrant labor patterns, community health, etc. **a. Output:** Propose the essential elements of the social context to account for in field studies and the role researchers can play in their amelioration. **i. Group Leader:** Donna Mergler, University of Quebec in Montreal (UQAM) **ii. Rapporteur:** Neil Pearce, London School of Hygiene & Tropical Medicine
	11. Approaches to surveillance of MeN **a. Objectives:** How best assess the cross-national burden of MeN, identify geographic or demographic "hot spots," and track the trends in MeN over time. **a. Output:** Propose administrative, hospital, or community-based measures for case-based and population-based measurement of MeN and potential ways to collaborate between governments and between government and academia. **i. Group Leader:** David H. Wegman, University of Massachusetts Lowell **ii. Rapporteur:** Ramón García-Trabanino, Hospital Nacional Rosales, El Salvador

Thursday, 19 November (continued)

11:15-12:30	**Poster Exhibition** 3-minute presentations, questions and time for individual review of posters
12:30-14:00	**Lunch**
Theme: How can we advance?	
14:00-15:30	**Working Groups (B) on Next Steps to Address Knowledge Gaps** *Participants will attend their other assigned Working Group for this second period of meetings. Group Leaders and Rapporteurs will remain the same for both sessions of the Working Groups.*
15:30-16:30	**Coffee Break (+ poster discussion)**
16:30-17:30	**Observations on the Context of the MeN Epidemic** **Chair:** Donna Mergler, University of Quebec in Montreal (UQAM)
	• **Precarious Populations: Impacts of the political and socio-economic context of the MeN epidemic** Ilana Weiss, La Isla Foundation, Nicaragua Jason Glaser, La Isla Foundation, Nicaragua

Friday, 20 November

08:15-08:30	Announcements and Explanation of the Day´s Activities
Theme: What are the top priority research initiatives?	
08:30-10:30	**Working group reports and discussions on concrete proposals for each theme** **Chair:** Christer Hogstedt, Karolinska Institutet, Sweden

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	Reports from each of the Working Group Leaders
	Moderated Discussion
10:30-10:45	**Coffee break**
10:45-12:00	**Moving forward – Priorities for a Research Agenda** Workshop summary and framework introducing a general discussion of a research agenda Chair: David Wegman, University of Massachusetts Lowell, USA Agnes Soares, PAHO/WHO, Washington DC Christer Hogstedt, Karolinska Institutet, Sweden Catharina Wesseling, Chair CENCAM, Karolinska Institutet, Sweden Ricardo Correa-Rotter, National Medical Science and Nutrition Institute, Mexico
	• Moderated Discussion
12:00-12:15	**Workshop Closing** Catharina Wesseling, Chair CENCAM, Karolinska Institutet, Sweden
12:15-13:30	**Lunch**
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13:30-15:00	**CENCAM General Assembly**

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