EDITORIAL

The Epidemic of Chronic Kidney Disease of Unknown Etiology in Mesoamerica: A Call for Interdisciplinary Research and Action

During the last 20 years, several regions in Central America and Mexico have seen a dramatic increase of a rapidly progressive chronic kidney disease, unexplained by diabetes and hypertension.[1–3] This regional epidemic of chronic kidney disease of unknown origin (CKDu) is also being referred to as the Mesoamerican nephropathy or MeN.[4] It has been estimated that this largely unknown epidemic has caused the premature death of at least 20 000 men.[3] In MeN-affected areas in Nicaragua[3] and Costa Rica (C. W., unpublished data, September 2011), chronic kidney disease mortality is up to fivefold the national rates. In El Salvador, kidney disease was the second most common cause of death among males in 2009.[5] MeN primarily, but not only, affects young and middle-aged male laborers in the agricultural sector, in particular sugarcane workers.[1–3]

Commonly victims of chronic kidney disease are not aware of their illness until the disease is in the final stages and their only treatment option is renal replacement therapy through dialysis or kidney transplantation. In developing nations, however, very few patients with end stage renal disease have access to renal replacement therapy, and most die without proper treatment.[6,7] The increase in CKD of conventional origin alone is a great burden for the health systems of developing countries, but in combination with the increase of CKDu in Mesoamerica it is overwhelming local health care systems to the point of collapse.[7]

Collaborative research efforts are thus a high priority to identify the etiology of MeN and develop prevention measures. With this objective, the university-based research and development Program on Work, Environment and Health in Central America (SALTRA; Programa Salud, Trabajo y Ambiente en América Central) organized an interdisciplinary workshop in Costa Rica, November 28–30, 2012. The goal was to identify present knowledge and gaps, and to elaborate methodological recommendations for future research. More than 50 researchers from 15 countries participated, with expertise in epidemiology, occupational health, public health, clinical and experimental nephrology, nephropathology, ecosystem health approaches, environmental sciences, social sciences, and law. The workshop benefitted from review articles that provided a summary of the current state of knowledge and working group reports that proposed recommendations and priorities for future research. A comprehensive technical and scientific workshop report is available at http://www.saltra.una.ac.cr/images/SALTRA/Documentacion/SerieSaludTrabajo/seriesaludytrabajo10.pdf. Highlights of the workshop findings are outlined here.

GEOGRAPHICAL OCCURRENCE

MeN is well identified in certain parts of Nicaragua, El Salvador, and Costa Rica, but not universally throughout these countries, and has not yet been documented by scientific reports in the rest of Mesoamerica. Increased rates of CKDu among agricultural workers are also reported in Sri Lanka[8] and India.[9] CKDu is probably a hitherto unrecognized global problem, although it is not clear if the CKDu epidemics observed in other parts of the world are the same disease or are caused by the same factors as in Mesoamerica.

LEADING HYPOTHESIS

Probably, there is more than one causal factor for CKDu in Mesoamerica, but important evidence exists to narrow hypotheses and focus future research and intervention efforts. Currently, the strongest hypothesis for MeN is that repeated heat exposure and dehydration resulting from strenuous work in tropical climates may be the key risk factor or an essential cofactor. These episodes are believed to lead to subclinical acute kidney injuries that develop into chronic damage over time.

The heat stress hypothesis is supported by results of epidemiological,[10] occupational hygiene,[11] experimental,[12] and biopsy[4] studies presented at the workshop by different research groups. In Nicaragua,[1,10] El Salvador,[2,10] and Costa Rica,[10] clearly the most affected populations are sugarcane cutters. Sugarcane cutters perform hard physical labor while exposed to extreme ambient heat (Figure 1).[11] There is some additional evidence for workers in other hot occupations.[1–3,10] Novel findings reported at the workshop included the first biopsy study in MeN cases from the region, demonstrating an unexpected mixed

FIGURE 1—Sugarcane harvesting in Nicaragua. Photograph by Tord Kjellström. Printed with permission.

pattern of glomerular and tubular sclerosis.[4] A mechanistically plausible link was proposed between dehydration and concomitant high nonsteroidal anti-inflammatory drug (NSAID) consumption (together a consequence of extreme ergonomic workloads), and subsequent kidney damage. Experimental data were presented showing induction of tubular kidney damage in mice exposed to repeated dehydration through the activation of the fructokinase-enzyme pathway in the kidney.[12] High fructose intake is commonly observed among workers who manage fluid replacement needs with popular sugared soft drinks providing further evidence for the biological plausibility of the dehydration hypothesis.

ALTERNATIVE HYPOTHESES AND COFACTORS

The workshop participants considered most well-known nephrotoxic agents to be unlikely single causes of MeN, but many merit further attention as potential cofactors through interactions or by influencing the progression of the disease. Primary cofactors considered were excess use of NSAIDs, inorganic arsenic, leptospirosis, and other nephrotoxic medications. Based on existing evidence, pesticides, hard water, and urinary tract infections are considered unlikely causes, but important to address because of community concerns and because addressing these is important for general public health. Of note, pesticides, arsenic, and hard water have been strongly hypothesized as etiologic factors for the CKDu epidemic in Sri Lanka. Lead, mercury, cadmium, uranium, and aristolochic acid are considered unlikely causes and of low research priority for MeN. Genetic susceptibility and childhood exposures that increase susceptibility may be important but have so far not been addressed. Most importantly, social determinants, including factors of work organization, migration patterns, and macro-socioeconomic drivers strongly influence disease occurrence and must be integrated in study designs.

RESEARCH PRIORITIES

The need for well-designed, interdisciplinary collaborative research was emphasized. Agreements on case definitions for clinical purposes and epidemiological research were seen to be of

utmost importance for maximizing the potential of future research, along with the development and validation of biomarkers of early and late disease. Priority attention should be on biopsy studies to elucidate pathophysiology, prevalence studies to further measure magnitude and identify new population groups at risk, and prospective cohort studies to advance etiologic research. Case-control studies can contribute to determining which hypotheses merit further exploration through cohort studies. Prospective cohort studies in occupational groups or contrasting communities should be pursued despite their high costs. Also, experimental research into biologic plausibility of hypothesized causes is needed.

INTERVENTIONS IN THE FACE OF UNCERTAIN ETIOLOGY

Although the etiology of MeN is uncertain, important interventions can be implemented that can be expected either to reduce the risk of developing chronic kidney disease or slow the progression of the disease. In workplace settings, it is important to reduce heat stress and to conduct controlled trials to improve hydration with adequate electrolyte replacement and safe drinking water, free of nephrotoxic metals and pesticides. Attention to treatment of existing CKDu is also a priority.

RESEARCH COLLABORATION

Interdisciplinary and multicenter research collaboration is undoubtedly desirable to address CKDu in Mesoamerica and epidemics elsewhere in the world. The workshop concluded with the establishment of the Consortium on the Epidemic of Nephropathy in Central America and Mexico (CENCAM), a research consortium to develop collaboration that builds upon the ongoing work in the region and the progress made at this meeting (see http://www.saltra.una.ac.cr/index.php/zoo/otros-proyectos/consorcio-de-investigacion-en-erc). The consortium model consists of a network of affiliated interdisciplinary scientific researchers working together to increase understanding and public awareness of the disease. CENCAM's activities target information sharing, compiling and disseminating research, facilitating collaboration in fund seeking, and serving as a bridge for translation of research results to policymakers.

DECLARATION

At the conclusion of the workshop, participants signed a declaration emphasizing the public health problem and the immediate need for prevention. Support is offered to governments to act now on existing knowledge and to local researchers and multisector actors to advance research through collaborative efforts. The declaration can be found on the Web site (http://www.saltra.una.ac.cr/index.php/statement).

CONCLUDING REMARKS

Although the etiology of the epidemic of chronic kidney disease in Mesoamerica remains unknown, it is known with certainty that the epidemic is present in several parts of Mesoamerica. This public health problem is of such magnitude and severity that urgent, comprehensive, and collaborative actions must be put into place to elucidate the cause(s), act on available information to prevent further disease, and find permanent solutions for prevention and mitigation. We hope the SALTRA workshop turned a corner in the history of this puzzling and expensive public health problem that ends the lives of the poorest workers in this region, prematurely and inequitably.

Finally, the workshop made it clear that this is likely not an isolated Mesoamerican problem, and similar epidemics are occurring elsewhere. If heat stress and related dehydration prove to be risk factors on their own or in combination with other factors, climate change will dramatically increase the population at risk in the near future.

Occupational heat stress–associated CKD is a global public health concern. Therefore, we are reaching out beyond Mesoamerica to increase international awareness about a regional problem with a possibly global scope, and we invite the international research and public health communities to combine efforts to urgently and efficiently address this problem. ■

Catharina Wesseling, MD, PhD
Jennifer Crowe, MSc
Christer Hogstedt, MD, PhD
Kristina Jakobsson, MD, PhD
Rebekah Lucas, PhD
David H. Wegman, MD, MSc

About the Authors

Catharina Wesseling and Jennifer Crowe are with the Program on Work, Environment and Health in Central America (SALTRA), Central American Institute for Studies on Toxic Substances (IRET), Universidad Nacional, Heredia, Costa Rica. Christer Hogstedt is with the Institute of Environmental Medicine (IMM), Karolinska Institutet, Stockholm, Sweden. Kristina Jakobsson is with the Department of Occupational and Environmental Medicine, Lund University, Lund, Sweden. Rebekah Lucas is with the Hothaps Program, Umeå International School of Public Health, Umeå University, Umeå, Sweden. David H. Wegman is with Work Environment, University of Massachusetts, Lowell.

Correspondence should be sent to Catharina Wesseling, Program on Work, Environment and Health in Central America (SALTRA), Central American Institute for Studies on Toxic Substances (IRET), Universidad Nacional, PO Box 86-3000, Heredia, Costa Rica (e-mail: inekewesseling@gmail.com). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted July 31, 2013.

doi:10.2105/AJPH.2013.301594

Contributors

The authors form the organizing committee of the 1st International Research Workshop on MeN and are the editors of the corresponding technical workshop report. Catharina Wesseling and Christer Hogstedt wrote the first draft of this editorial, which was edited by the remaining members of the group. The final version was approved by all authors.

Acknowledgments

The authors acknowledge the contributions of the participants of the 1st International Research Workshop on MeN; November 28–30, 2012; San José, Costa Rica. The workshop was partially funded by the Universidad Nacional in Costa Rica and the European Union through support to the SALTRA Program, as well as by the workshop participants who paid their own way to the meeting.

References

1. Torres C, Aragón A, González M, et al. Evidence of widespread chronic kidney disease of unknown cause in Nicaragua, Central America. *Am J Kidney Dis.* 2010;55:485–496.

2. Peraza S, Wesseling C, Aragón A, et al. Decreased kidney function among agricultural workers in El Salvador. *Am J Kidney Dis.* 2012;59:531–540.

3. Ramirez-Rubio O, McClean MD, Amador JJ, Brooks DR. An epidemic of chronic kidney disease in Central America: an overview. *J Epidemiol Community Health.* 2013;67:1–3.

4. Wijkström J, Leiva R, Elinder CG, et al. Clinical and pathological characterization of Mesoamerican Nephropathy: a new kidney disease in Central America. *Am J Kidney Dis.* Epub ahead of print July 10, 2013.

5. DIGESTYC. Indicadores demográficos. Ministry of Economy of El Salvador. 2013. Available at: http://www.digestyc.gob.sv/index.php/servicios/descarga-de- documentos/category/47-presentaciones-estadisticas-sociales.html. Accessed July 23, 2013.

6. Kirby T. Screening for chronic kidney disease shows promise. *Lancet.* 2010;375(9722):1240–1241.

7. Leiva R. The health system and CKD in El Salvador. In: Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D (eds). *Mesoamerican Nephropathy: Report From the First International Research Workshop on MeN.* Heredia, Costa Rica: SALTRA/IRET-UNA; 2013, 219–220.

8. Athuraliya NT, Abeysekera TD, Amerasinghe PH, et al. Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. *Kidney Int.* 2011;80: 1212–1221.

9. Jakobsson K. Chronic kidney disease of unknown origin in India. In: Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D (eds). *Mesoamerican Nephropathy: Report From the First International Research Workshop on MeN.* Heredia, Costa Rica: SALTRA/IRET-UNA; 2013, 57–58.

10. Brooks D, Ramírez-Rubio O. Epidemiology of CKD of unknown causes in Mesoamerica In: Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D (eds). *Mesoamerican Nephropathy: Report From the First International Research Workshop on MeN.* Heredia, Costa Rica: SALTRA/IRET-UNA; 2013, 59–60.

11. Crowe J, Wesseling C, Román Solano B, et al. Heat exposure in sugarcane harvesters in Costa Rica. *Am J Industrial Med.* Medicine. Epub ahead of print June 17, 2013.

12. Johnson RJ, Roncal C, Correa-Rotter R, et al. Fructose and kidney disease. In: Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D (eds). *Mesoamerican Nephropathy: Report From the First International Research Workshop on MeN.* Heredia, Costa Rica: SALTRA/IRET- UNA; 2013, 117–118.