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Special Report

Resolving the Enigma of the Mesoamerican Nephropathy: A Research Workshop Summary

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The First International Research Workshop on Mesoamerican Nephropathy (MeN) met in Costa Rica in November 2012 to discuss how to establish the extent and degree of MeN, examine relevant causal hypotheses, and focus efforts to control or eliminate the disease burden. MeN describes a devastating epidemic of chronic kidney disease of unknown origin predominantly observed among young male sugarcane cutters. The cause of MeN remains uncertain; however, the strongest hypothesis pursued to date is repeated episodes of occupational heat stress and water and solute loss, probably in combination with other potential risk factor(s), such as nonsteroidal anti-inflammatory drug and other nephrotoxic medication use, inorganic arsenic, leptospirosis, or pesticides. At the research workshop, clinical and epidemiologic case definitions were proposed in order to facilitate both public health and research efforts. Recommendations emanating from the workshop included measuring workload, heat, and water and solute loss among workers; quantifying nephrotoxic agents in drinking water and food; using biomarkers of early kidney injury to explore potential causes of MeN; and characterizing social and working conditions together with methods for valid data collection of exposures and personal risk factors. Advantages and disadvantages of different population study designs were detailed. To elucidate the etiology of MeN, multicountry studies with prospective cohort design, preferably integrating an ecosystem health approach, were considered the most promising. In addition, genetic, experimental, and mechanistic methods and designs were addressed, specifically the need for kidney biopsy analysis, studies in animal models, advances in biomarkers, genetic and epigenetic studies, a common registry and repository of biological and demographic data and/or specimens, and other areas of potential chronic kidney disease experimental research. Finally, in order to improve international collaboration on MeN, workshop participants agreed to establish a research consortium to link these Mesoamerican efforts to other efforts worldwide.

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During the last 20 years, several regions in Central America have seen a dramatic increase in rapidly progressive chronic kidney disease (CKD) unexplained by conventional risk factors such as diabetes and hypertension and concentrated in relatively young men, particularly sugarcane workers.[1] In November 2012, the Program on Work, Health and Environment in Central America (SALTRA) organized an international research workshop on this Mesoamerican nephropathy (MeN) designed to review the present knowledge of MeN and similar epidemics elsewhere, set research priorities, and establish international collaborations.

Much work has been done in the 8 years since the first SALTRA workshop on MeN[2]: studies from Central America have been published and there also is evidence suggesting MeN-like kidney diseases in several countries in Asia. Much more remains to be done. The disease has yet to be characterized in Guatemala, Honduras, Panama, and Mexico, as well as in regions of Nicaragua, El Salvador, and Costa Rica, the 3 Mesoamerican countries in which MeN has been well documented.[3-6] We need to characterize the patterns and trends of the disease in all these settings and better understand prevalence in populations that are less well studied or not identified as high risk, such as women and adolescents. Future studies should forcefully target elucidating the cause of MeN and promote interventions, and simultaneously attract international funding for the problem.

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Our objective here is to reflect the workshop's considerations and agreements on how best to establish the extent and degree of MeN, examine relevant causal hypotheses, and focus efforts to control or eliminate the disease burden. This information is intended to benefit future studies.

MOVING FORWARD WITH POPULATION STUDIES

Of particular interest for population studies is agreeing on a case definition for MeN, which priority exposures to focus on, methods to measure exposures and personal risk factors, and study design selection.

Defining a Case

There are different objectives to defining a case, for both clinical diagnosis and use in population studies of early or predisease.

Clinical Case Definition

A basic clinical definition for patients with MeN was reasonably agreed on: persons living in Mesoamerica who have abnormal kidney function, per internationally accepted standards (KDIGO [Kidney Disease: Improving Global the Outcomes] 2012 guidelines[7]), with no other known causes—for example, diabetes, hypertension, or polycystic kidney disease—for their CKD. MeN patients have low kidney function, frequently have hypokalemia, and typically have no hypertension or edema on physical examination. Clinical diagnosis is reasonably standardized (see Box 1).

Epidemiologic Case Definition

In epidemiologic studies, a case definition based on criteria emanating from a composite clinical case definition may be valuable for descriptive purposes: for example, it may be used to calculate the need for medical care in the community. However, if the aim of an epidemiologic study is to explore risk and susceptibility factors, the clinical definition falls short because it emphasizes the advanced disease stage. Instead, several different components should be investigated with focus on both early and more advanced signs of adverse effects. Although there is not yet definitive agreement on criteria, the following basic considerations can be stated:

- A creatinine assay, which is traceable to a reference method based on isotope-dilution mass spectrometry[8]
- The CKD-EPI (CKD Epidemiology Collaboration) formula for estimating glomerular filtration rate (GFR), which is evaluated in multiple ethnicities[9] and in accordance with the recent KDIGO 2012 guidelines[7]
- A semiquantitative dipstick for proteinuria; a morning spot sample is best but may be impractical. The nature and timing of samples should be reported for proper interpretation. If possible, albumin-creatinine ratio in urine should be determined because it corrects for the effect of body water loss on the level of proteinuria
- The KDIGO 2012 guidelines[7] should be used for "quasi staging" only. Proteinuria, serum creatinine level, and estimated GFR should always be reported separately and as multiple (not binary) categories
- Information on hypertension and diabetes, at a minimum self-report on health care provider diagnosis

Box 1. Elements Needed for Clinical Diagnosis

Necessary

- History: Clinical history, family history, information about work, liquid intake, medication including NSAIDs intake
- Physical examination: Blood pressure, edema
- Blood tests: Electrolytes, hemoglobin, eGFR (SCr, cystatin C), uric acid, glucose
- Urine samples: Proteinuria, hematuria, biomarkers for tubular damage such as NAG, α_1-microglobulin, β_2-microglobulin

Desirable

- Imaging studies: Ruling out polycystic kidney disease
- Kidney biopsy: Light microscopy, immunofluorescence, electron microscopy

Abbreviations: eGFR, estimated glomerular filtration rate; NAG, *N*-acetyl-β-D-glucosaminidase; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine.

Measuring Nephrotoxic Exposures

There is no single study that will allow us to investigate the many different exposures that are hypothesized to be associated with MeN due to the different agents of interest, the potential for both occupational and nonoccupational exposure, and the different objectives to be addressed by the research. Because all these factors will influence the design of a study, a conceptual model was developed to summarize the different ways in which exposure could be characterized and related to disease status (Fig 1).

The general consensus of the workshop was that repeated heat exposure, water and solute loss (by dehydration or volume depletion), and strenuous work in tropical climates may be key risk factors or essential cofactors.[1] Many other exposures were considered as alternative hypotheses, potential cofactors interacting with body water loss, or disease progression factors, in particular, excess use of nonsteroidal anti-inflammatory drugs (NSAIDs), fructose consumption in rehydration fluids, inorganic arsenic, leptospirosis, pesticides, and hard water.

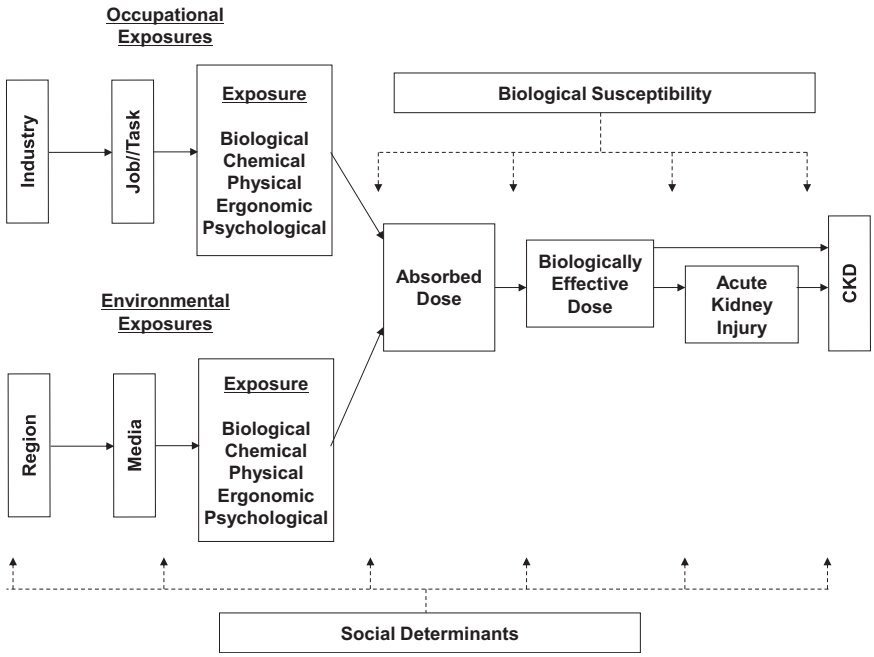

Figure 1. Conceptual model for exposure-related disease. Exposures from both work and general environments are received by each individual in a unique manner. The complex of exposures are experienced directly as "dose" or are transformed into an effective dose that can lead to chronic kidney disease (CKD). The course of pathophysiologic changes that result in CKD may occur directly, as a slow continuum that gradually affects kidney function, or the development of CKD may follow from a series of repeated clinical or subclinical kidney disease episodes that do not completely resolve and ultimately cause irreversible kidney disease. It is important to recognize that either route to CKD is affected by individual susceptibility factors and that social determinants play a role in mediating the impact of any exposure or dose.

Exposure assessment will need to document media source(s), exposure pathways, and levels of exposure through a range of assessment tools consistent with the exposures to be assessed, from quantification of physical and chemical hazards in the work and general environment to biomarkers and questionnaires to characterize present and past personal exposures. It is important to examine potential interactions between the prioritized exposures. Major occupational and environmental concerns, along with exposure assessment methods, are workload, heat exposure, dehydration and volume depletion, nephrotoxic agents, biomarkers of exposure, and questionnaires.

Workload

Two types of workload assessments were considered: physiologic measurements and qualitative methodologies. Heart rate can be used as a physiologic measure of workload as well as relative intensity, and it is fairly inexpensive and convenient for field testing. Heart rate data can be supplemented by a qualitative assessment of work done by, for example, measuring productivity (ie, quantity of material produced in a given time under specific conditions) or using international standards or recommendations (from bodies such as the International Organization for Standardization or the Occupational Safety and Health Administration) to estimate metabolic load.

Heat Exposure

Workplace heat exposure can be measured as: (1) immediate ambient conditions, (2) general ambient conditions, and (3) internal body core temperature. The immediate worksite ambient environment can be assessed accurately, but requires specialized equipment and validated heat stress indexes, for example, the wet bulb globe temperature.[10] General environmental conditions can be assessed using data from existing local weather stations and converted, with some assumptions, to the wet bulb globe temperature. Measuring internal body core temperature in field settings requires specialized equipment and is valid for only the single individual's response to heat exposure.

Dehydration and Volume Depletion

Markers of water or solute loss or fluid balance range from urine and blood markers to changes in body weight and blood pressure. Change in body weight was considered the least expensive and most reliable means of determining an individual's fluid balance. However, this method presents difficulties in the field with finding a flat solid surface for the scales to rest on and privacy for participants.[11] Urinary measures (specific gravity and osmolality) are sensitive to only large acute changes in fluid balance and lag behind plasma osmolality measures.[12] Therefore, it is recommended that urinary measures be used to assess hydration status on a day-to-day basis.[13]

Nephrotoxic Agents

Affected communities are highly concerned about the quality of the drinking water, in particular possible pesticide contamination and water hardness. Even if these agents may not be risk factors for MeN, ensuring that these communities have access to clean drinking water certainly is a worthwhile endeavor

from a broader public health perspective. The workshop participants agreed that, among the various environmental sources of exposure to populations at risk, characterizing drinking water and food should be the highest priority, with inorganic arsenic and pesticides (particularly those that are known to cause acute kidney injury) as highest priority agents. Recent experimental evidence suggests that information for consumption of bottled drinks or foods containing fructose also should be collected.[14]

In addition to the occupational and environmental causal factors, personal use of nephrotoxic medication, such as aminoglycoside antibiotics, and long-term use of NSAIDs must be assessed. The use of these drugs is common and uncontrolled in Central America. Traditional medicines based on herbs or other natural ingredients also are used in the region and may be of concern. Finally, infectious agents in general were judged to be unlikely causes, with the exception of leptospirosis.

Biomarkers of Exposure

In addition to quantification of nephrotoxic hazards in the media of the work and general environment, food and drinking water, and external personal exposures, a biomarker of total absorbed dose (generally using blood, urine, hair, or nails) is important for assessing personal exposure to these agents. Such biomarkers can provide information about exposures across multiple exposure routes in both occupational and nonoccupational settings. However, variability in exposure over time is a critically important consideration during study design. Single measurements only provide information about exposure over a short period, unless the biological half-life is long or the exposure is routine and constant.

Questionnaires

Carefully constructed and, if possible, validated questionnaires remain an invaluable tool for characterizing personal exposures, particularly with regard to the past and when biomarkers of long-term exposure are not available. Questionnaires should be especially designed to enhance recall and can be used to gather information on work and/or residential histories, including daily amount, frequency, and type of fluid consumed at work over time, historical pesticide exposures, diet history, and personal risk factors (discussed next). Standardizing data collection tools in different studies in different countries will facilitate comparisons of research results and accelerate the research progress.

Measuring Personal Risk Factors

As with the exposures mentioned in the previous section, when measuring any personal factors in population studies, a well-defined protocol is necessary, with a specific role designated to each individual involved in taking measurements during data collection, training, supervision, and quality control. Personal risk factors that can influence the disease or need to be collected for outcome estimation along with methodological measurement issues, are body mass and height, nutritional status and eating/drinking habits, smoking, alcohol and drug consumption, medical and family disease history, and medication/self-medication.

Body Mass and Height

Measuring mass requires reliable scales that can tolerate high temperature and humidity, calibrated before and at the site of study. Measuring height requires a flat surface and, if possible, a measuring device with a sliding arm that rests on the participant's head.

Nutritional Status and Eating/Drinking Habits

There already exists a wealth of resources and data on the nutritional value of specific foods. In questionnaires that ask about current nutrition, it is important to train interviewers about the meaning of portion size. The use of common utensils together with a measuring cup will help participants estimate volumes of food and liquids consumed. This could be particularly useful to assess dietary fructose.

Smoking and Alcohol and Drug Consumption

There are standard questions, but if these habits are suspected of being connected with the disease being studied, there is a tendency to under-report them. It is important to find and validate colloquial ways of asking these questions and use qualitative methods to get more information about traditions. Age- and sex-appropriate interviewers (possibly from similar communities) can improve the validity of responses.

Medical and Family Disease History

Information about comorbid conditions is best when obtained from medical records, which is difficult in Central America. Alternatively, participants can be asked if they have been given a diagnosis by a care provider, particularly if hypertension or diabetes has been diagnosed. Obtaining the history of urolithiasis (there may be a common cause such as repeated dehydration/volume depletion) and urinary tract infections is important. Family history of CKD should be documented.

Medication/Self-medication

For information on medication use in communities, investigators should research drug use in areas of interest prior to the start of the study, including the local use of herbal medications. The researcher then can bring samples of the most commonly used medications and ask people to pick the ones they use and ask about quantity.

Social and Working Conditions

An essential part of understanding the drivers of the epidemic of CKD of unknown origin is to understand the contributing social and work factors. Therefore, we need systematic identification of potential social determinants (social factors and working conditions) that might be contributing causal factors to the epidemic. Identifying social determinants requires understanding who makes up the workforce, migration patterns, length of a work day, alternative employment/activities, and periods of unemployment. Further, studying the different working conditions for contracted and subcontracted workers could shed light on the distribution of contributing factors of the disease. Other variables to consider assessing include education, access to health care, and poverty. For social factors in particular, standardizing data collection across countries to create a database of comparable data in all countries in which there is an excess of MeN cases would be invaluable.

CONSIDERATIONS IN SELECTING THE DESIGNS OF POPULATION STUDIES

Population studies offer great promise for elucidating the nature and natural history of MeN and opportunities for prevention. Each of the available approaches brings advantages and disadvantages, so the workshop reviewed all approaches and summarized what each has to offer.

Cross-sectional Studies

This approach can be applied equally well in general populations or specific occupational groups to characterize the prevalence of kidney disease and relevant factors. To better understand the magnitude of the problem, the workshop proposed cross-sectional surveys in at least 4 countries in Mesoamerica. The sampling frame should represent geographic, sex, and occupational distributions of special interest among both rural and urban populations. Emphasis should be directed to heat stress and it is important to start including women (including those doing strenuous jobs in hot environments) as well as children and teenagers. Family-based designs within communities should be encouraged.

These studies will rely heavily on questionnaires that should include core questions for all countries in addition to specific questions by country. Concerning occupational history, it is important to investigate occupations that have a high prevalence of disease in concert with occupations associated with a low prevalence. Questions related to amounts of drinking water (including sources and quality), fructose drinks, heat stress, and history of signs and symptoms of dehydration/volume depletion, as well as exposure to pesticides and other nephrotoxic agents, should be included. Medical history should emphasize, at minimum, the history of urinary tract pathologies (infections and lithiasis), transmittable diseases, and NSAID use.

As for objective measures, physical examination should include anthropometric measures and blood pressure. At least single urine and blood samples should be obtained with early-morning samples. For work populations, measurements also should be made at the end of the work shift, if feasible.

Cohort Studies

A number of design and logistical issues regarding implementation of a cohort study to investigate the causes of MeN were explored, leading to the conclusion that despite the efficiencies of a retrospective cohort study, a prospective study would be necessary to capture the important exposure and covariate information. In order to lay the groundwork for a cohort study of the required magnitude, preliminary studies will be needed to: (1) accurately and efficiently measure exposure factors of interest and identify populations that would provide variation in exposure, and (2) demonstrate that it is possible to retain a sufficient proportion of participants during the follow-up period.

Study Population and Nature of Cohort

A cohort based on the identification of a group of people considered exposed as well as a group considered not exposed ensures that the targeted exposure(s) are well represented. It requires a smaller number of participants if a group with high exposures can be identified. For an occupational hypothesis, such as heat exposure/strenuous work or agrichemical exposure, such groups could be identified and enrolled. Given the prominence of occupational heat stress as a hypothesis, occupationally based cohorts that reflect a range of exposure levels might be advantageous. However, access to occupational cohorts may prove difficult.

Alternatively, targeting higher and lower risk geographic areas could serve as a substitute. Selecting general populations from different areas with different primary types of work could provide the variation in exposure levels needed for an effective study. Such an approach has been used for prevalence studies in Nicaragua and El Salvador,[3,4] where certain geographic locations were used to represent different types of economic activities and climatic conditions.

The study population should be relatively young to increase the likelihood that cases of CKD represent the early stages of the disease. It also would be best if the study population was drawn from different countries to ensure the detection of common risk factors driving this international epidemic among

diverse populations, while at the same time local conditions can be examined. Preferably, testing should occur every year to allow for early diagnosis, information on natural history, contact to reduce loss to follow-up, and updates of exposure status.

Outcomes

The primary outcome would be CKD or cause of death. Secondary outcomes would be biomarkers of kidney injury, with specific biomarkers to be determined based on feasibility and suspect exposures.

Major Determinants and Exposures

Potential factors that could be assessed in such a study, whether occupationally or residentially based, include life-long residential and occupational history of climate, ergonomic, and chemical exposures; fluid consumption at work and home; fructose intake; inorganic arsenic exposure; use of pharmaceuticals (particularly NSAIDs) and natural remedies; diseases of the urinary tract; infectious diseases; pesticides; and possibly others.

Prestudies to Assess Potential

Follow-up studies of previous (and in most cases published) cross-sectional studies would clarify the problems and potentials for tracing investigated persons over 3-5 years, as well as indicate disease progression of, for example, CKD stages 2-3 and the possibility to validate and test new CKD markers. Investigating high and low prevalence areas of hypothesized risk exposures would provide necessary information for power calculations and choosing study populations for a prospective study. Attention could be directed to exploring the feasibility of assessing targeted exposures, such as heat and exertion, by creating an appropriate job-exposure matrix.

Case-Control Studies

Case-control studies were judged to have limited value for understanding the cause due to difficulty collecting historical information on specific exposures and/or low prevalence of specific exposures among cases and controls. At present, current methods for identifying cases in an otherwise healthy population are not conducive to identifying cases of early or subclinical disease.

However, a case-control study has considerably lower time and monetary costs and could contribute to determining which hypotheses merit further exploration through prospective cohort designs. Under these circumstances, case-control studies may be more useful in population-based rather than industry-based studies, potentially as part of a multicenter cross-national study to evaluate risk factors in a population that is not restricted to a specific occupational group and includes women and younger populations, groups that are understudied to date. With respect to case-control investigation, it remains crucial that case definitions are consistent and clear across different studies in different settings and countries.

Intervention Studies

Interventions designed to eliminate only one risk factor associated with MeN are difficult to design when the cause is poorly understood. Nonetheless, it is clear that working in hot conditions, body water loss, and use of NSAIDs are reasonably established risks for those in early stages of CKD. Therefore, we suggest small well-controlled studies comparing ordinary/present with optimal/adjusted intake of water and salt during heavy hot work, such as during the sugarcane zafra (harvest), replicated in multiple worksites and countries.

Intervention studies have the additional complication of addressing community beliefs about causality of factors such as pesticides or unsafe water. Participatory research (ie, research that gets participants involved in the water sampling and the decisions with the experts about where to sample and when) is one way to help address this challenge. Researchers must be acutely aware that workers may risk being fired and blacklisted as a result of screening results. Additionally, because harvesters usually are paid by the amount of cane they cut, provisions must be made to ensure that workers who participate in the study do not lose income.

Working With an Ecosystem Perspective

Although male sugarcane workers have been in focus as a group at high risk, other populations also may be affected, albeit inadequately investigated. Neither risk factors nor protective factors are yet understood. Therefore, an ecosystem approach to human health, coupled with spatial epidemiology and a life-cycle perspective, was introduced as a methodology that could assist in better understanding the environmental, biological, and social factors that contribute to and/or influence the development of CKD. An ecosystem approach is intervention driven and builds on the convergence of expertise in the health, social, and natural sciences to conceptually map a transdisciplinary understanding of the clinical, subclinical, and infraclinical (ie, physiologic alterations that occur in an apparently healthy individual to maintain homeostasis but, if prolonged, may lead to a disease state) disease patterns within a particular geo-spatially defined ecosystem.

From a life-cycle perspective, it is important to consider possible fetal exposures, parents' health status, childhood living conditions, and age at which a person started working, all of which may contribute to the development of the disease (Fig 2[15]). At each stage in this life cycle, social, environmental, and

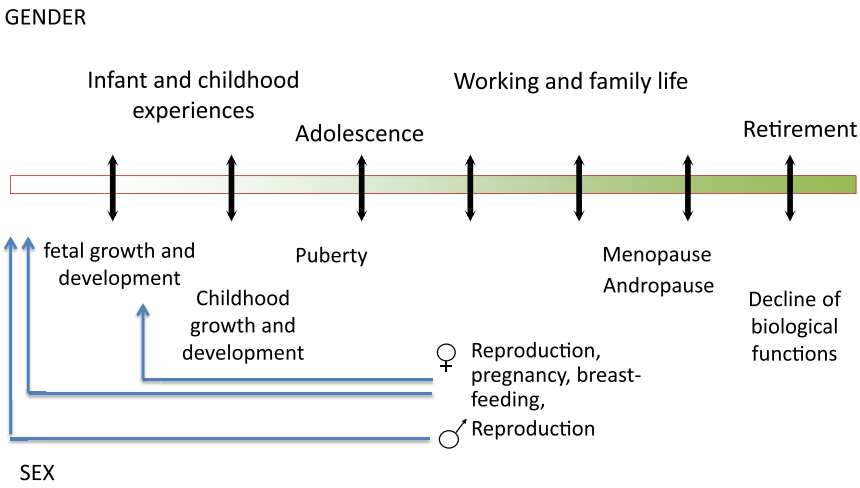

Figure 2. A schematic representation of the lifecycle, with an emphasis on gender (social construct) and sex (biological differences). Reproduced with permission from Mergler 2012.[15]

biological factors may contribute to the development of, or protection from, CKD.

Finally, an ecosystem approach incorporates concerns with the broader macro drivers. Such concerns include, for example, the World Bank policies for loans to extend sugarcane growing, corporate greed that results in poorly paid workers who are already living in extreme poverty, lack of workers' organizations, and lack of human rights.

A practical need is to develop a conceptual framework with an eco-health perspective around MeN and its determinants, risk factors, causal pathways, and hypotheses in this region. In order to implement an ecosystem lifecycle approach, the following actions need to be undertaken:

- Identify an area of concern (eg, illness, toxins, and type of industry), particularly for which there is previous information
- Delimit the spatial boundaries of this ecosystem and the populations living within its boundaries
- Examine, within this ecosystem and with these populations, the main physical, health, economic, and social drivers
- Initiate studies to examine the pathways between potential exposures throughout the life cycle, the factors that influence these exposures, and health outcomes; involve communities and other stakeholders in both the design and solutions

GENETIC, EXPERIMENTAL, MECHANISTIC, AND METHODS RESEARCH

Although the main focus of the workshop was epidemiologic research, other disciplines also were discussed.

Genetic and Epigenetic Studies

Genetic and epigenetic studies may provide important information with respect to the genetic susceptibility of Mesoamericans to different environmental factors. A genome-wide non–hypothesis-driven research model may be most successful in identifying such a gene or gene complex. Should a genetic susceptibility be identified in Mesoamericans, this genotype could be introduced into an animal model to assess the impact of different environmental risk factors on the pathogenesis of CKD.

Studies in Animal Models

Animal models can provide important information concerning specific agents and the synergistic interactions of different environmental risk factors. Such interactions might include, for example, water and solute loss in combination with arsenic, fructose, NSAIDs, or hard water. In this manner, we could better isolate environmental effects that would inform clinical practice and epidemiologic studies.

Kidney Biopsy Analysis

To date there have been an extremely limited number of CKD kidney biopsy specimens analyzed in MeN. Biopsy results show interesting preliminary findings.[16] Given the potential clues to pathophysiology/etiology, carefully planned biopsies should be performed, but only when safety is guaranteed and patients, especially in early stages, can be followed up with good clinical practice to improve quality of life.

A Common Registry and Repository

A multilateral biobank that could store urine samples, serum samples, and DNA would be extremely beneficial. This would enable sample storage for future analysis with advanced techniques and understanding. However, specimen collection needs to be considered carefully and followed uniformly. Also, ethical consideration of participant consent to prospective sample testing has to be adhered to. This

would be an expensive undertaking, requiring a large amount of funding. Similarly, a common database or registry would promote collaboration and advancement in the field of CKD. This is much less expensive and should be a priority action.

Other Areas of Potential CKD Experimental Research

Opportunities should be considered to explore kidney injury further in populations without hypertension or diabetes. For example, in elite athletes who consume high volumes of fluid and sugar and repeatedly are exposed to high heat load.

Advances in Biomarkers

Studies to identify subclinical kidney injury and biomarkers might be useful in defining the pathophysiology, natural history, and early clinical detection of CKD; possible treatment; and as surrogate end points in intervention studies. Early urinary markers of acute and chronic tubular injury should be sought to improve on albumin as a marker, that is, β_2-microglobulin, clusterin, cystatin C, kidney injury molecule-1 (Kim-1), trefoil factor 3, neutrophil gelatinase-associated lipocalin (NGAL), and others.[17,18] A number of emerging technologies have enabled researchers to measure several proteins in a single urine sample rapidly and reliably so that large numbers of samples can be run and analyzed in a high-throughput manner. Cystatin C in serum also may provide a more accurate measure for estimating GFR. There also is a need to develop biomarkers for better detection of exposures, such as pertinent agrichemicals and infections. Biomarkers of susceptibility should be considered based on genetic approaches.

ORGANIZING FOR THE FUTURE

The participants aim to capitalize on the momentum and progress of the workshop discussions in order to improve international collaboration on MeN epidemiologic, medical and intervention, or policy research initiatives, as well as to consolidate as a group. To that end, workshop participants of this working group agreed on the following stated objective: To formalize collaboration that builds upon the ongoing work in the region and the progress that we have made at this meeting. A research consortium is being created to link these efforts to others around the globe (http://www.saltra.una.ac.cr/index.php/zoo/otros-proyectos/consorcio-de-investigacion-en-erc). We hope that the extraordinary efforts made by the participants in this workshop will continue through the consortium, maximizing the potential of research initiatives to solve the devastating public health issue of MeN.

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