Research & Perspectives on Chronic Kidney Disease of Uncertain Etiology in International Journals

The following abstracts, in alphabetical order by article title, were culled by ***MEDICC Review***'s research team. We welcome additions from peer-reviewed journals, in order to make the list as comprehensive and current as possible. Send title, abstract and URL to: editors@medicc.org Proceedings of meetings (unless published in peer-reviewed journals), grey literature and press coverage are not included.

Aetiological factors of Chronic Kidney Disease in the North Central Province of Sri Lanka: A review of evidence to-date. Wanigasuriya K. J College Commun Physicians Sri Lanka. 2012 Jun;17(1):15–20.

Introduction Chronic kidney disease of unknown aetiology is a major health care problem in the North Central Province of Sri Lanka. During the last decade several researches were undertaken to identify the prevalence and aetiology of the disease. Fifteen manuscripts published in peer-reviewed scientific journals and two peer reviewed abstracts of were included in the review. **Results** The disease mainly affects males from poor socio-economic backgrounds who are involved in paddy farming. Mild proteinuria was present but urinary sediments were normal. Renal biopsies were reported as interstitial nephritis. Significant predictors of kidney disease in these patients included age, history of smoking, being under treatment for hypertension and drinking well water in the fields. Studies on heavy metal and ochratoxin exposure have revealed conflicting results. Fluoride content of well water in all these areas exceeded the WHO recommended level of o.6 mg/L. Water in all areas was alkaline which could facilitate mobilization of fluoride from minerals indicating a fluoride mediated mechanism for renal damage. **Conclusion** The aetiology of CKDu in NCP of Sri Lanka is probably multi-factorial involving one or more environmental factors and a possible genetic predisposition in vulnerable populations.

An epidemic of chronic kidney disease in Central America: an overview. Ramirez O, McClean MD, Amador JJ, Brooks DR. Postgrad Med J. 2013 Mar;89(1049):123–5. No abstract available.

Assessment of long-term and recent pesticide exposure among rural school children in Nicaragua. Rodriguez T, van Wendel de Joode B, Lindh CH, Rojas M, Lundberg I, Wesseling C. Occup Environ Med. 2012 Feb;69(2):119–25.

Objective This study assessed pesticide exposure of children in rural Nicaragua in relation to parental pesticide use, from around conception to current school age, as part of an epidemiological evaluation of neurodevelopment effects. **Methods** We included 132 children whose parents were subsistence farmers or plantation workers, or had an agricultural history. As proxies for children's long-term exposures, we constructed cumulative parental pesticide-specific use indices for periods before and after the child's birth from data obtained using an icon-calendar-based questionnaire, of application hours (h) for plantation workers and subsistence farmers, and of kilograms of active ingredients (ai) only for subsistence farmers. Pesticide residues of TCPY, 3-PBA and 2,4-D were analysed in children's urine as indicators for current exposures. **Results** Life-time indices were highest for the organophosphates chlorpyrifos (median 114 h (min 2; max 1584), 19.2 kg ai (min 0.37; max 548)) and methamidophos (84 h (6; 1964), 12.2 kg ai (0.30; 780)). The P50 values of children's urinary residues were 3.7 µg/g creatinine for TCPY, 2.8 for 3-PBA and 0.9 for 2,4-D; TCPY values are comparable with those in other countries, but 3-PBA and 2,4-D are considerably higher. The maximum levels for all three pesticides are the highest reported for children. Residues increased on days after application, but most high residue levels were unrelated to parental pesticide applications. **Conclusion** Urinary pesticide residues reveal high environmental exposure among children in rural Nicaragua. The quantitative parental pesticide use indices as proxies for children's exposures during different periods may be useful for the evaluation of developmental health effects.

Association between occupational heat stress and kidney disease among 37,816 workers in the Thai Cohort Study (TCS). Tawatsupa B, Lim LL, Kjellstrom T, Seubsman SA, Sleigh A; Thai Cohort Study Team. J Epidemiol. 2012;22(3):251–60.

Background We examined the relationship between self-reported occupational heat stress and incidence of self-reported doctor-diagnosed kidney disease in Thai workers. **Methods** Data were derived from baseline (2005) and follow-up (2009) self-report questionnaires from a large national Thai Cohort Study (TCS). Analysis was restricted to full-time workers (n = 17 402 men and 20 414 women) without known kidney disease at baseline. We used logistic regression models to examine the association of incident kidney disease with heat stress at work, after adjustment for smoking, alcohol drinking, body mass index, and a large number of

socioeconomic and demographic characteristics.**Results** Exposure to heat stress was more common in men than in women (22% vs 15%). A significant association between heat stress and incident kidney disease was observed in men (adjusted odds ratio [OR] = 1.48, 95% CI: 1.01-2.16). The risk of kidney disease was higher among workers reporting workplace heat stress in both 2005 and 2009. Among men exposed to prolonged heat stress, the odds of developing kidney disease was 2.22 times that of men without such exposure (95% CI 1.48-3.35, P-trend <0.001). The incidence of kidney disease was even higher among men aged 35 years or older in a physical job: 2.2% exposed to prolonged heat stress developed kidney disease compared with 0.4% with no heat exposure (adjusted OR = 5.30, 95% CI 1.17-24.13). **Conclusions** There is an association between self-reported occupational heat stress and self-reported doctor-diagnosed kidney disease in Thailand. The results indicate a need for occupational health interventions for heat stress among workers in tropical climates.

Chronic kidney disease and associated risk factors in the Bajo Lempa region of El Salvador: Nefrolempa Study, 2009. Orantes CM, Herrera R, Almaguer M, Brizuela E, Hernández CE, Bayarre H, et al. MEDICC Rev. 2011 Apr;13(4):14–22.

Introduction In El Salvador, end-stage renal disease is the leading cause of hospital deaths in adults, the second cause of death in men and the fifth leading cause of death in adults of both sexes in the general population. Objective Identify risk factors for chronic kidney disease and urinary markers of renal and vascular damage, measure kidney function and characterize prevalence of chronic kidney disease in persons aged ≥18 years in the Bajo Lempa region of El Salvador. **Methods** A cross-sectional analytical epidemiological study was carried out using active screening for chronic kidney disease and associated risk factors in individuals aged ≥18 years in the Bajo Lempa Region, a rural, coastal area in El Salvador. Door-to-door visits and clinical examinations were conducted. Epidemiological and clinical data were collected including: family and personal clinical history of disease; biological, behavioral, social and environmental risk factors; physical measurements; urinalysis for markers of renal and vascular damage; and blood tests (serum creatinine, serum glucose, lipid profile). Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula. Chronic kidney disease case confirmation was done three months later. Multiple logistic regression was used for data analysis.**Results** A total of 375 families and 775 individuals (343 men, 432 women) were studied-88.3% of the total resident population in the region. Elevated prevalence of risk factors was observed: diabetes mellitus, 10.3%; hypertension,16.9%; family history of chronic kidney disease, 21.6%; dyslipidemias, 63.1%; overweight, 34%; obesity, 22.4%; metabolic syndrome, 28.8%; use of non-steroidal anti-inflammatory drugs, 74.8%; infectious diseases, 86.9%; agricultural occupation, 40.6% (80.6% in men); and contact with agrochemicals, 50.3% (82.5% in men). Prevalence renal damage markers was 15.8% (greater in men): microalbuminuria 6.3%; proteinuria 5.7%; hematuria 3.5%; proteinuria-hematuria 0.3%. Proteinuria of <1 g/L predominated. Prevalence of chronic kidney disease was 17.9% (25.7% in men; 11.8% in women). Distribution by stages: stage 1, 4.6%; stage 2, 3.5%; stage 3, 6.2%; stage 4, 3.0%; stage 5, 0.6%. In patients with chronic kidney disease, most common was non-diabetic chronic kidney disease (86.3%), followed by chronic kidney disease associated with neither diabetes nor hypertension (54.7%). Prevalence of chronic renal failure was 9.8% (17% in men; 4.1% in women). Multiple logistic regression showed significant association with increasing age, male sex, hypertension and family history of chronic kidney disease. **Conclusions** Elevated prevalence of chronic kidney disease, chronic renal failure and risk factors was found, compared to international reports. Most common was chronic kidney disease of unknown cause, associated with neither diabetes nor hypertension. Associations were found with age, male sex, hypertension and family history of chronic kidney disease, with decline in kidney function beginning at early ages. Male farmers have a dual burden of non-traditional (occupational, toxic environmental) and traditional (vascular) risk factors that could act in synergy, contributing to kidney damage.

Chronic Kidney Disease and Associated Risk Factors in Two Salvadoran Farming Communities, 2012. Vela XF, et al. MEDICC Rev. 2014 Apr;16(2). Submitted.

Chronic kidney disease in Costa Rica. Cerdas M. Kidney Int Suppl. 2005 Aug;(97):S31–3.

Costa Rica is one of the Central American countries, located between Nicaragua to the north and Panama to the south. Like other Latin American countries, Costa Rica deals with social and economic problems associated with poverty, except for one significant difference-Costa Rica has not had an army since 1948, and so the people and government can spend more money on education and health. For this reason, Costa Rica is very different from other Latin American countries. We do not need weapons, and we have had a democratic tradition for 100 years. Despite our economic and social limitations, Costa Ricans have universal access to a health system that covers 98% of the inhabitants. Renal replacement therapy (RRT) is accessible to all who need it. In the last 5 years, Costa Rica has doubled the number of patients on hemodialysis, and has the

highest number of kidney transplants per million population (pmp) in Latin America, with 20.63 transplants pmp in 2000, 27.25 transplants pmp in 2001, and 24.81 transplants pmp in 2002. However, the prevalence of all forms of RRT in Costa Rica is currently 193 pmp. This suggests that end-stage renal disease is underdiagnosed in Costa Rica as it is in many other Latin American countries. Greater research efforts are needed to determine the true extent of renal disease in Costa Rica and to optimize the use of health-sector resources to provide a better and more robust program of RRT for patients with end-stage renal disease.

Chronic Kidney Disease in Disadvantaged Populations. Martins D, Agodoa L, Norris K. Int J Nephrol. 2012;2012:469265. doi: 10.1155/2012/469265.

Disadvantaged populations across the globe exhibit a disproportionate burden of chronic kidney disease (CKD) because of differences in CKD occurrence and outcomes. Although many CKD risk factors can be managed and modified to optimize clinical outcomes, the prevailing socioeconomic and cultural factors in disadvantaged populations, more often than not, militate against optimum clinical outcomes. In addition, disadvantaged populations exhibit a broader spectrum of CKD risk factors and may be genetically predisposed to an earlier onset and a more rapid progression of chronic kidney disease. A basic understanding of the vulnerabilities of the disadvantaged populations will facilitate the adaptation and adoption of the kidney disease treatment and prevention guidelines for these vulnerable populations. The purpose of this paper is to examine recent discoveries and data on CKD occurrence and outcomes in disadvantaged populations and explore strategies for the prevention and treatment of CKD in these populations based on the established guidelines.

Chronic kidney disease in Latin America: time to improve screening and detection. Cusumano AM, González MC. Clin J Am Soc Nephrol. 2008 Mar;3(2):594–600.

Latin America is a conglomerate of adjacent countries that share a Latin extraction and language (Spanish or Portuguese) and exhibit extreme variations in socioeconomic status. End-stage renal disease prevalence and incidence rates have been growing steadily, probably as a result of the increase in life expectancy, aging of the population, a growing epidemic of type 2 diabetes, and a fast epidemiologic transition across the region. Chronic noncommunicable diseases impose an enormous cost, barely supported at present and unlikely afforded by Latin America in the future. National health surveys in Chile, Mexico, and Argentina showed a high prevalence of cardiovascular risk factors. A total of 21% of the Chilean population had a creatinine clearance <80 ml/min. Among the surveyed people, 8.6% of Argentines, 14.2% of Chileans, and 9.2% of Mexicans had proteinuria. There are ongoing national chronic kidney disease detection programs in Brazil, Cuba, Peru, Uruguay, and Venezuela; Argentina, Colombia, Bolivia, Dominican Republic, Guatemala, and Paraguay are still developing them. The prevalence of cardiovascular and renal risk factors is high in Latin America. Data about chronic kidney disease are scarce, but public health awareness is high, evidenced by ongoing or developing chronic kidney disease detection programs. High-risk patients (e.g., those with hypertension or diabetes, elderly) must be studied, using simple determinations such as creatinine and proteinuria. For these programs to succeed, lifestyle changes must be encouraged and public awareness must be increased through teaching and media-oriented activities.

Chronic kidney disease in Nicaragua: a qualitative analysis of semi-structured interviews with physicians and pharmacists. Ramirez O, Brooks DR, Amador JJ, Weiner DE, Kaufman JS, Scammell MK. BMC Public Health. 2013 Apr 16;13:350.

Background Northwestern Nicaragua has a high prevalence of chronic kidney disease (CKD) of unknown cause among young adult men. In addition, frequent occurrence of urinary tract infections (UTI) among men and a dysuria syndrome described by sugarcane workers as "chistata" are both reported. This study examines health professionals´ perceptions regarding etiology of these conditions and their treatment approaches, including use of potentially nephrotoxic medications. **Methods** Nineteen in-person semi-structured interviews were conducted in November 2010 among ten physicians and nine pharmacists practicing in the region. **Results** Health professionals perceived CKD as a serious and increasing problem in the region, primarily affecting young men working as manual laborers. All interviewees regarded occupational and environmental exposure to sun and heat, and dehydration as critical factors associated with the occurrence of CKD. These factors were also considered to play a role in the occurrence of chistata in the region. Health professionals indicated that reluctance among workers to hydrate might be influenced by perceptions of water contamination. Symptoms often were treated with non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and antibiotics. Physicians acknowledged that the diagnosis of UTI usually was not based on microbial culture and opined that the use of potentially nephrotoxic medications may be contributing to CKD. **Conclusions** Interviews provided evidence suggesting that medications such as diuretics, antibiotics and NSAIDs are widely used and sold over the counter for symptoms that may be related to dehydration and volume depletion. These factors, alone or in combination, may be possible contributors to kidney damage.

Acute kidney damage coupled with volume depletion and exposures including medications and infectious agents should be further evaluated as causal factors for CKD in this region.

Chronic Kidney Disease in our Farming Communities: Implications of an Epidemic. Rodríguez MI. MEDICC Rev. 2014 Apr;16(2). Submitted.

Chronic kidney disease in the Arab world: a call for action. Farag YM, Kari JA, Singh AK. Nephron Clin Pract. 2012;121(3–4):c120–3.

Chronic kidney disease (CKD) is an emerging non-communicable disease worldwide. The Arab countries have a high prevalence of CKD risk factors, e.g. diabetes, obesity and hypertension. Unfortunately, the magnitude of CKD in the Arab world has not been studied well. This review presents the current data on CKD in the Arab world and proposes a call for action to address this rising epidemic.

Chronic Kidney Disease in the Developing World. Barsoum RS. N Engl J Med. 2006 Mar 9;354(10):997–9.

The attention being paid globally to chronic kidney disease is attributable to five factors: the rapid increase in its prevalence, the enormous cost of treatment, recent data indicating that overt disease is the tip of an iceberg of covert disease, an appreciation of its major role in increasing the risk of cardiovascular disease, and the discovery of effective measures to prevent its progression. These factors render chronic kidney disease an important focus of health care planning even in the developed world, but the problems they delineate in the developing world are far more challenging. Some 85 percent of the world's population live in low-income or middle-income countries, where the clinical, epidemiologic, and socioeconomic effects of the disease are expected to be the greatest.

Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. Jayatilake N, Mendis S, Maheepala P, Mehta FR; CKDu National Research Project Team. BMC Nephrol. 2013 Aug 27;14:180.

Background This study describes chronic kidney disease of uncertain aetiology (CKDu), which cannot be attributed to diabetes, hypertension or other known aetiologies that has emerged in the North Central region of Sri Lanka. **Methods** A cross-sectional study was conducted, to determine the prevalence of and risk factors for CKDu. Arsenic, cadmium, lead, selenium, pesticides and other elements were analysed in biological samples from individuals with CKDu and compared with age- and sex-matched controls in the endemic and non-endemic areas. Food, water, soil and agrochemicals from both areas were analysed for heavy metals. **Results** The age-standardised prevalence of CKDu was 12.9% (95% confidence interval [CI] = 11.5% to 14.4%) in males and 16.9% (95% CI = 15.5% to 18.3%) in females. Severe stages of CKDu were more frequent in males (stage 3: males versus females = 23.2% versus 7.4%; stage 4: males versus females = 22.0% versus 7.3%; $P < 0.001$). The risk was increased in individuals aged >39 years and those who farmed (chena cultivation) (OR [odds ratio] = 1.926, 95% CI = 1.561 to 2.376 and OR = 1.195, 95% CI = 1.007 to 1.418 respectively, $P < 0.05$). The risk was reduced in individuals who were male or who engaged in paddy cultivation (OR = 0.745, 95% CI = 0.562 to 0.988 and OR = 0.732, 95% CI = 0.542 to 0.988 respectively, $P < 0.05$). The mean concentration of cadmium in urine was significantly higher in those with CKDu (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. Urine cadmium sensitivity and specificity were 70% and 68.3% respectively (area under the receiver operating characteristic curve = 0.682, 95% CI = 0.61 to 0.75, cut-off value ≥0.397 μg/g). A significant dose-effect relationship was seen between urine cadmium concentration and CKDu stage ($P < 0.05$). Urine cadmium and arsenic concentrations in individuals with CKDu were at levels known to cause kidney damage. Food items from the endemic area contained cadmium and lead above reference levels. Serum selenium was <90 μg/l in 63% of those with CKDu and pesticides residues were above reference levels in 31.6% of those with CKDu. **Conclusions** These results indicate chronic exposure of people in the endemic area to low levels of cadmium through the food chain and also to pesticides. Significantly higher urinary excretion of cadmium in individuals with CKDu, and the dose-effect relationship between urine cadmium concentration and CKDu stages suggest that cadmium exposure is a risk factor for the pathogenesis of CKDu. Deficiency of selenium and genetic susceptibility seen in individuals with CKDu suggest that they may be predisposing factors for the development of CKDu.

Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. Chandrajith R, Nanayakkara S, Itai K, Aturaliya TN, Dissanayake CB, Abeysekera T, et al. Environ Geochem Health. 2011 Jun;33(3):267–78.

The increase in the number of chronic kidney disease (CKD) patients from the north central region of Sri Lanka has become an environmental health issue of national concern. Unlike in other countries where long-standing diabetes and hypertension are the leading causes of renal diseases, the majority of CKD patients from this part of Sri Lanka do not show any identifiable cause. As the disease is restricted to a remarkably specific geographical terrain, particularly in the north central dry zone of the country, multidisciplinary in-depth research studies are required to identify possible etiologies and risk factors. During this study, population screening in the prevalent region and outside the region, analysis of geoenvironmental and biochemical samples were carried out. Population screening that was carried out using a multistage sampling technique indicated that the point prevalence of CKD with uncertain etiology is about 2–3% among those above 18 years of age. Drinking water collected from high-prevalent and non-endemic regions was analyzed for their trace and ultra-trace element contents, including the nephrotoxic heavy metals Cd and U using ICP-MS. The results indicate that the affected regions contain moderate to high levels of fluoride. The Cd contents in drinking water, rice from affected regions and urine from symptomatic and non-symptomatic patients were much lower indicating that Cd is not a contributing factor for CKD with uncertain etiology in Sri Lanka. Although no single geochemical parameter could be clearly and directly related to the CKD etiology on the basis of the elements determined during this study, it is very likely that the unique hydro geochemistry of the drinking water is closely associated with the incidence of the disease.

Chronic kidney disease of unknown aetiology in Sri Lanka: is cadmium a likely cause?Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R. BMC Nephrol. 2011 Jul 5;12:32.

Background The rising prevalence of chronic kidney disease (CKD) and subsequent end stage renal failure necessitating renal replacement therapy has profound consequences for affected individuals and health care resources. This community based study was conducted to identify potential predictors of microalbuminuria in a randomly selected sample of adults from the North Central Province (NCP) of Sri Lanka, where the burden of CKD is pronounced and the underlying cause still unknown. **Methods**Exposures to possible risk factors were determined in randomly recruited subjects (425 females and 461 males) from selected areas of the NCP of Sri Lanka using an interviewer administered questionnaire. Sulphosalicylic acid and the Light Dependent Resister microalbumin gel filtration method was used for initial screening for microalbuminuria and reconfirmed by the Micral strip test. **Results** Microalbuminuria was detected in 6.1% of the females and 8.5% of the males. Smoking ($p < 0.001$), alcohol use ($p = 0.003$), hypertension ($p < 0.001$), diabetes ($p < 0.001$), urinary tract infection (UTI) ($p = 0.034$) and consumption of water from wells in the fields ($p = 0.025$) were associated with microalbuminuria. In the binary logistic regression analysis, hypertension, diabetes mellitus, UTI, drinking well water in the fields, smoking and pesticide spraying were found to be significant predictors of microalbuminuria.**Conclusions** Hypertension, diabetes mellitus, UTI, and smoking are known risk factors for microalbuminuria. The association between microalbuminuria and consumption of well water suggests an environmental aetiology to CKD in NCP. The causative agent is yet to be identified. Investigations for cadmium as a potential causative agent need to be initiated.

Chronic kidney disease of unknown aetiology in the North Central Province of Sri Lanka: trying to unravel the mystery. Wickremasinghe AR, Peiris-John RJ, Wanigasuriya KP. Ceylon Med J. 2011 Dec;56(4):143–6. No abstract available.

Chronic Kidney Disease of Unknown Cause in Agricultural Communities Around the World. Almaguer M, et al. MEDICC Rev. 2014 Apr;16(2). Submitted

Chronic Kidney Disease of Unknown Etiology: A Disease Related to Global Warming? Johnson RJ, et al. MEDICC Rev. 2014 Apr;16(2). Submitted.

Chronic Kidney Disease of Unknown Etiology Should Be Renamed Chronic Agrochemical Nephropathy. Jayasinghe S. MEDICC Rev. 2014 Apr;16(2). Submitted.

CKD in Central American Agricultural Communities: Challenges for Epidemiology and Public Health. Silva LC, Ordúñez P. MEDICC Rev. 2014 Apr;16(2). Submitted.

CKDu: Strategies for Saving Lives Now. Glaser J, Weiss I. MEDICC Rev. 2014 Apr;16(2). Submitted.

Chronic renal failure among farm families in cascade irrigation systems in Sri Lanka associated with elevated dietary cadmium levels in rice and freshwater fish (Tilapia). Bandara JM, Senevirathna DM, Dasanayake DM, Herath V, Bandara JM, Abeysekara T, et al. Environ Geochem Health. 2008 Oct;30(5):465–

78.

Chronic renal failure (CRF), in the main agricultural region under reservoir based cascade irrigation in Sri Lanka has reached crisis proportion. Over 5,000 patients in the region are under treatment for CRF. The objective of this study is to establish the etiology of the CRF. Concentrations of nine heavy metals were determined in sediments, soils of reservoir peripheries, water and Nelumbo nucifera (lotus) grown in five major reservoirs that supply irrigation water. All five reservoirs carried higher levels of dissolved cadmium (Cd), iron (Fe) and lead (Pb). Dissolved Cd in reservoir water ranged from 0.03 to 0.06 mg/l. Sediment Cd concentration was 1.78-2.45 mg/kg. No arsenic (As) was detected. Cd content in lotus rhizomes was 253.82 mg/kg. The Provisional Tolerable Weekly Intake (PTWI) of Cd based on extreme exposure of rice is 8.702-15.927 microg/kg body weight (BW) for different age groups, 5-50 years. The PTWI of Cd due to extreme exposure of fish is 6.773-12.469 microg/kg BW. The PTWI on a rice staple with fish is 15.475-28.396 microg/kg BW. The mean urinary cadmium (UCd) concentration in CRF patients of age group 40-60 years was 7.58 microg Cd/g creatinine and in asymptomatic persons UCd was 11.62 microg Cd/g creatinine, indicating a chronic exposure to Cd. The possible source of Cd in reservoir sediments and water is Cd-contaminated agrochemicals. The CRF prevalent in north central Sri Lanka is a result of chronic dietary intake of Cd, supported by high natural levels of fluoride in drinking water, coupled with neglecting of routine de-silting of reservoirs for the past 20 years.

Chronic renal failure in North Central Province of Sri Lanka: an environmentally induced disease. Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R, Hittarage A. Trans R Soc Trop Med Hyg. 2007 Oct;101(10):1013–7.

This study was conducted to determine the aetiology of chronic renal failure (CRF) in the North Central Province of Sri Lanka. Patients (n=183) with CRF of unknown aetiology were compared with controls (n=200) who had no evidence of chronic renal dysfunction. Exposure to possible risk factors were determined by an interviewer-administered questionnaire. Being a farmer (P<0.001), using pesticides (P<0.001), drinking well water (P<0.001), a family history of renal dysfunction (P=0.001), use of ayurvedic treatment (P<0.001) and a history of snake bite (P<0.001) were risk factors for CRF of unknown aetiology. Using logistic regression analysis, a family history of chronic renal disease, taking ayurvedic treatment and history of snake bite were found to be significant predictors for CRF of unknown aetiology. There is evidence to support an environmental aetiology to CRF in Sri Lanka.

Chronic renal failure in Sri Lanka caused by elevated dietary cadmium: Trojan horse of the green revolution. Bandara JM, Wijewardena HV, Liyanege J, Upul MA, Bandara JM. Toxicol Lett. 2010 Sep 15;198(1):33–9.

The endemic of chronic renal failure (CRF) emerged in 2002 in the farming provinces of Sri Lanka. An estimate of dietary cadmium intake was between 15 and 28 microg/kg body weight per week. The mean urinary cadmium in patients diagnosed with stage 5 kidney failure was 7.6 microg/g creatinine and 11.6 microg/g for asymptomatic persons. The agrochemical triple superphosphate (TSP) fertilizer containing 23.5-71.7 mg Cd/kg was the source of cadmium added to soils. Mean Cd content in cultivated vs. uncultivated soils in Anuradhapura district was 0.02 +/- 0.01 vs. 0.11 +/- 0.19 mg/kg while in Polonnaruwa district, it was 0.005 +/- 0.004 vs. 0.016 +/- 0.005 mg/kg. Prior to the Green Revolution, the amount of fertilizer used in rice cultivation in 1970 was 32,000 metric tons (Mts) rising to 74,000 Mts in 1975. Up to 68.9 Mts of Cd could have entered into the rice-cascade reservoir environment from TSP use since 1973. Diversion of the Mahaweli River in 1970-1980 further increased cadmium input. Cadmium transfer from Upper Mahaweli water to Polgolla was 72.13 kg/day. Cadmium content of the sediments from reservoirs collecting cadmium from irrigated TSP fertilized crop fields (rice and vegetables) was 1.8-2.4 mg/kg.

Clinical and Pathological Characterization of Mesoamerican Nephropathy: A New Kidney Disease in Central America. Wijkström J, Leiva R, Elinder CG, Leiva S, Trujillo Z, Trujillo L, et al. Am J Kidney Dis. 2013 Nov;62(5):908–18.

Background An endemic of chronic kidney disease (CKD) of unknown cause among rural inhabitants in Central America has been identified. Young and otherwise healthy men working in plantations are frequently affected. The name Mesoamerican nephropathy (MeN) has been suggested. Clinically, MeN presents with low-grade proteinuria and progressive kidney failure. The renal pathology of this disease has not yet been described. **Study Design** Case series. **Setting & Participants** 8 male patients with CKD of unknown cause and clinically suspected MeN were recruited from a nephrology unit in El Salvador. All recruited patients had been working on plantations. Kidney biopsies, blood, and urine samples were collected. **Outcomes & Measurements** Renal morphology examined with light microscopy, immunofluorescence, and electron

microscopy; clinical and biochemical characteristics.**Results** A similar pattern was seen in all 8 biopsy specimens, with extensive glomerulosclerosis (29%-78%) and signs of chronic glomerular ischemia in combination with tubular atrophy and interstitial fibrosis, but only mild vascular lesions. Electron microscopy indicates podocytic injury. Biochemical workup showed reduced estimated glomerular filtration rate (27-79 mL/min/1.73 m2 with the CKD Epidemiology Collaboration [CKD-EPI] creatinine equation), low-grade albuminuria, and increased levels of tubular injury biomarkers. Hypokalemia was found in 6 of 8 patients. **Limitations** Small number of patients from one country. **Conclusions** This study is the first report of the biochemical and morphologic findings in patients with MeN. Our findings indicate that MeN constitutes a previously unrecognized kidney disease with damage to both glomerular and tubulointerstitial compartments. **Clinical Characteristics of Chronic Kidney Disease of Nontraditional Causes in Salvadoran Farming Communities**. Herrera R, et al. MEDICC Rev. 2014 Apr;16(2). Submitted.

Could ochratoxin A in food commodities be the cause of chronic kidney disease in Sri Lanka?Wanigasuriya KP, Peiris H, Ileperuma N, Peiris-John RJ, Wickremasinghe R. Trans R Soc Trop Med Hyg. 2008 Jul;102(7):726–8.

Ochratoxin A (OA) is a naturally occurring mycotoxin with nephrotoxic properties that can contaminate plant food products. OA concentrations were assessed in commonly consumed food items in the North Central Province of Sri Lanka, where chronic kidney disease is diagnosed at epidemic proportions. Ninety-eight randomly selected food samples were analysed. Mycotoxin was detected in the extract by using a MycoMonitor Ochratoxin A ELISA assay kit (Helica Biosystems Inc., USA). The levels of OA found in these food commodities were below the recommended statutory maximum limit and are unlikely to be a potential risk factor for nephropathy in the North Central Province of Sri Lanka.

Decreased kidney function among agricultural workers in El Salvador. Peraza S, Wesseling C, Aragón A, Leiva R, García RA, Torres C, et al. Am J Kidney Dis. 2012 Apr;59(4):531–40.

Background An epidemic of chronic kidney disease of unknown cause has emerged along the Pacific coast of Central America, particularly in relatively young male sugarcane workers. In El Salvador, we examined residence and occupations at different altitudes as surrogate risk factors for heat stress. **Study Design** Cross-sectional population-based survey. **Setting & Participants** Populations aged 20-60 years of 5 communities in El Salvador, 256 men and 408 women (participation, 73%): 2 coastal communities with current sugarcane and past cotton production and 3 communities above 500 m with sugarcane, coffee, and service-oriented economies. **Predictor** Participant sex, age, residence, occupation, agricultural history by crop and altitude, and traditional risk factors for CKD. **Outcomes** Serum creatinine (SCr) level greater than the normal laboratory range for sex, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2, and proteinuria categorized as low (protein excretion ≥30-<300 mg/dL) and high grade (≥300 mg/dL). **Results** Of the men in the coastal communities, 30% had elevated SCr levels and 18% had eGFR <60 mL/min/1.73 m2 compared with 4% and 1%, respectively, in the communities above 500 m. For agricultural workers, prevalences of elevated SCr levels and eGFR <60 mL/min/1.73 m2 were highest for coastal sugarcane and cotton plantation workers, but were not increased in sugarcane workers at 500 m or subsistence farmers. Women followed a weaker but similar pattern. Proteinuria was infrequent, of low grade, and not different among communities, occupations, or sexes. The adjusted ORs of decreased kidney function for 10-year increments of coastal sugarcane or cotton plantation work were 3.1 (95% CI, 2.0-5.0) in men and 2.3 (95% CI, 1.4-3.7) in women. **Limitations** The cross-sectional nature of the study limits etiologic interpretations. **Conclusion** Agricultural work on lowland sugarcane and cotton plantations was associated with decreased kidney function in men and women, possibly related to strenuous work in hot environments with repeated volume depletion.

Decreased kidney function of unknown cause in Nicaragua: a community-based survey. Torres C, Aragón A, González M, López I, Jakobsson K, Elinder CG, et al. Am J Kidney Dis. 2010 Mar;55(3):485–96.

Background End-stage kidney disease overwhelms health services in Central America. We determined prevalences of decreased kidney function in distinct populations in the most affected region of Nicaragua. **Study design** Cross-sectional survey. **Setting & Participants** Total populations aged 20-60 years of 5 villages in Northwest Nicaragua: mining/subsistence farming (elevation, 100-300 m above sea level), banana/sugarcane (100-300 m), fishing (0-100 m), services (0-100 m), and coffee (200-675 m); 479 men and 617 women (83% response). Predictor or factor Village; participant sex, age, and occupation; conventional chronic kidney disease risk factors. **Outcomes** Serum creatinine (SCr) values greater than laboratory reference range for sex, estimated glomerular filtration rate <60 mL/min/1.73 m(2), proteinuria stratified in the low (dipstick protein excretion, 30-300 mg/dL) and high (>300 mg/dL) range. **Results** Prevalences of abnormal SCr levels: 18% (of all men) and 5% (of all women); in the mining/subsistence farming village, 26% and 7%; banana/sugarcane, 22% and 6%; fishing, 13% and 4%; services, 0% and 1%; and coffee, 7% and 0%.

Prevalences of estimated glomerular filtration rate <60 mL/min/1.73 m(2): 14% (of all men) and 3% (of all women); in the listed villages, 19% and 5%, 17% and 4%, 10% and 2%, 0% and 0%, and 7% and 0%, respectively. Proteinuria, predominantly in the low range, affected 14% and 11% of all men and women without marked differences between villages. By occupation, abnormal SCr levels occurred in 31% and 24% of male and female agricultural workers at 100-300 m above sea level, but not at higher altitudes, and also was high in male artisans (43%), construction workers (15%), and miners (14%). In logistic regression models, for the banana/sugarcane and mining/subsistence farming villages, high blood pressure and age were significant predictors of abnormal SCr levels in men, and for mining/subsistence farming, age in women. **Limitations** Causality is not addressed. **Conclusions** In some Nicaraguan villages and population segments, men in particular show a high prevalence of decreased kidney function of unknown origin, possibly environmental or occupational.

End-stage renal disease among patients in a referral hospital in El Salvador. Trabanino RG, Aguilar R, Silva CR, Mercado MO, Merino RL. Rev Panam Salud Publica. 2002 Sep;12(3):202–6. Spanish, English.

ObjectiveEl Salvador is a country with high mortality from end-stage renal disease (ESRD). The objective of this study was to determine the epidemiological characteristics of a series of new cases of ESRD seen in a referral hospital in the country.**Methods**A cross-sectional study was conducted of all the new cases that initiated chronic dialysis between November 1999 and March 2000. Using a personal interview, data were obtained on the patients' clinical, demographic, and occupational characteristics, among others.**Results** During the five months that the study lasted, 205 new cases of ESRD were observed. Among the 202 interviewees, two groups were clearly distinguished. One group, of 67 patients (33%), had known risk factors for ESRD, similar to those for developed countries (basically, diabetes mellitus, hypertension, and chronic consumption of non-steroidal anti-inflammatories). Another group of 135 patients (67%) had unusual characteristics that were not associated with the known risk factors. The majority of the patients in this second group were male, farmers, residents of coastal areas or areas next to rivers, and some years before had been exposed, without adequate protection, to agricultural insecticides or pesticides through their work.**Conclusions**We have identified an important group of patients with ESRD who seem to lack a cause for their disease. Their special characteristics make it possible to suspect a relationship with the occupational exposure to insecticides or pesticides. New studies are needed in order to confirm this hypothesis.

Environmental Factors Incriminated in the Development of End Stage Renal Disease in El-Minia Governorate, Upper Egypt. Kamel EG, El-Minshawy O. Int J Nephrol Urol. 2010;2(3):431–7.

Background and Aims End Stage Renal Disease (ESRD) has various causes that differ according to patient's country. In Egypt it is a huge health problem with high prevalence in El-Minia governorate as 308 per million population suffer from it. The aim of the work is to investigate the possible causes of ESRD with an unknown etiology in El-Minia Governorate. **Methods**A total number of 216 patients with an unknown etiology of ESRD as well as 220 controls were interviewed using a structured questionnaire including information about environmental factors predicted to cause ESRD such as occupation, pesticide handling, and source of drinking water. **Results**Distribution of patients by residence showed that most patients lived in rural areas (76%), compared to 57% in controls ($p<0.001$). Drinking unsafe water was reported by 72% of patients and 48% of controls ($p<0.001$). Family history of renal disease was found among 10% of patients and 4% of controls ($p<0.001$). Exposure to pesticides and using herbs for the treatment were more among patients than controls (52% Vs 14% respectively) and (34% Vs 6% respectively) ($p<0.001$). **Conclusions**ESRD with an unknown etiology may be attributed to environmental factors such as drinking unsafe water, exposure to pesticides and using herbs for treatment. Educational programs for common people should be strengthened. Lead pipes water supplies should be changed. Use of any herbs should be prohibited except under the supervision of Ministry of Health.

Epidemiology of chronic kidney disease in a Sri Lankan population: experience of a tertiary care center. Wijewickrama ES, Weerasinghe D, Sumathipala PS, Horadagoda C, Lanarolle RD, Sheriff RM. Saudi J Kidney Dis Transpl. 2011 Nov;22(6):1289–93.

Chronic kidney disease (CKD) is a growing problem in Sri Lanka. Diabetes and hypertension are the main contributors to the disease burden. A new form of CKD of uncertain etiology (CKD-u) is the predominant form of CKD in certain parts of Sri Lanka, threatening to reach epidemic proportions. A cross-sectional descriptive study was carried out over a three-month period at the National Hospital of Sri Lanka to identify the underlying etiologic factors for the disease in a cohort of patients with CKD. A total of 200 patients were studied with a mean age of 50.57 years. Of them, 108 (54%) were in CKD stage V. Majority of the patients were from the western province (137, 68.5%) with only five (2.5%) from provinces with high prevalence of CKD-u. The most common underlying causes of CKD were diabetes (88, 44%) and hypertension (34, 17%). However, in patients

younger than 40 years of age the most common cause was glomerulonephritis (20, 42.6%). Diabetes was the most common cause of CKD among patients from the western province (74, 54%). The prevalence of CKD-u was twice as high in patients from areas outside the western province compared with patients from this province ($P > 0.05$). The low prevalence of CKD-u in the study population could be the result of poor representation of patients from provinces with high prevalence of CKD-u.

Epidemiology of Chronic Kidney Disease of Unknown Cause in Salvadoran Agricultural Communities. Orantes CM, et al. MEDICC Rev. 2014 Apr;16(2). Submitted.

Evidence of tubular damage in the very early stage of chronic kidney disease of uncertain etiology in the North Central Province of Sri Lanka: a cross-sectional study. Nanayakkara S, Senevirathna ST, Karunaratne U, Chandrajith R, Harada KH, Hitomi T, et al. Environ Health Prev Med. 2012 Mar;17(2):109–17.

Background In the North Central Province of Sri Lanka, chronic kidney disease of uncertain etiology (CKDue) has increased markedly over the past 15-20 years. **Methods** From around 4,700 patients who were followed up, 106 affected patients who visited two local clinics in the endemic area for CKDue on August 10, 2009 and 10 pedigrees of 10 of these cases with familial clustering of CKDue participated in this study. Urine samples, collected from affected patients (n = 106), unaffected relative controls (n = 81), and Japanese controls (n = 50), were analyzed for two tubular markers: α1-microglobulin and N-acetyl-β-D: -glucosaminidase. Urine samples from patients with CKDue stages 1-4 (n = 101) and all the samples from unaffected relatives and Japanese controls were analyzed for urinary cadmium concentration**. Results** Urinary excretion of α1-microglobulin was elevated even in the earliest stage of CKDue compared with its levels in unaffected relative controls. Urinary excretion of N-acetyl-β-D: -glucosaminidase was elevated only in stage 5. In contrast, urinary cadmium excretion was similar in CKDue patients and in the unaffected relative controls, and levels in both these groups were significantly lower than the level in the Japanese controls. All levels were below the threshold level for renal toxicity, indicating the absence of any evidence of cadmium toxicity. **Conclusions** The present study indicates that renal tubular damage occurs in the very early stage of CKDue and demonstrates the existence of familial clustering, suggesting that CKDue is likely to be the outcome of exposure to an unknown nephrotoxin in susceptible subjects in the endemic region.

Exposure to acetylcholinesterase-inhibiting pesticides and chronic renal failure. Peiris-Jhon RJ, Wanigasuriya JK, Wickeremasinghe AR, Dissanayake WP, Hittarage A. Ceylon Med J. 2006 Mar;51(1):42–3.
Recent reports show an increase in the incidence of end-stage renal disease of unknown aetiology from the North-Central Province of Sri Lanka [1]. As the majority of the patients are from rural farming communities, pesticide exposure is suspected as a cause, although it is not a proven aetiological factor for chronic renal failure (CRF). Acetylcholinesterase (AChE)-inhibiting insecticides are the most widely used pesticides in Sri Lanka. Although nephrotoxicity is not recognised as a clinical feature of anticholinesterase poisoning, there are reports of acute renal failure provoked by acute tubular necrosis [2] and rhabdomyolysis [3] following high dose OP exposure. This preliminary study was conducted to determine if there is an association between CRF of unknown aetiology and organophosphate (OP) exposure.

Fructokinase activity mediates dehydration-induced renal injury
Roncal CA, Ishimoto T, Lanaspa MA, Rivard CJ, Nakagawa T, Ejaz AA, et al. Kidney Int. 2013 Dec 11.

The epidemic of chronic kidney disease in Nicaragua (Mesoamerican nephropathy) has been linked with recurrent dehydration. Here we tested whether recurrent dehydration may cause renal injury by activation of the polyol pathway, resulting in the generation of endogenous fructose in the kidney that might subsequently induce renal injury via metabolism by fructokinase. Wild-type and fructokinase deficient mice were subjected to recurrent heat-induced dehydration. One group of each genotype was provided water throughout the day and the other group was hydrated at night, after the dehydration. Both groups received the same total hydration in 24 h. Wild-type mice that received delayed hydration developed renal injury, with elevated serum creatinine, increased urinary NGAL, proximal tubular injury, and renal inflammation and fibrosis. This was associated with activation of the polyol pathway, with increased renal cortical sorbitol and fructose levels. Fructokinase-knockout mice with delayed hydration were protected from renal injury. Thus, recurrent dehydration can induce renal injury via a fructokinase-dependent mechanism, likely from the generation of endogenous fructose via the polyol pathway. Access to sufficient water during the dehydration period can protect mice from developing renal injury. These studies provide a potential mechanism for Mesoamerican nephropathy.

Geographical distribution of chronic kidney disease of unknown origin in North Central Region of Sri Lanka. Jayasekara JM, Dissanayake DM, Adhikari SB, Bandara P. Ceylon Med J. 2013 Mar;58(1):6–10.

Objectives In early nineties investigators noticed an alarmingly high incidence of an apparently new form of chronic kidney disease of unknown aetiology (CKD-U) in some parts of Sri Lanka. The aim of the study was to investigate the geographical distribution of CKD-U using GIS and GPS mapping. **Methods**Community based information was collected from 11,630 patients for GIS mapping using ARC 9.2 software. Based on GIS mapping, two locations were selected for GPS mapping to locate the households of 863 CKD-U patients with reference to reservoirs, irrigation canals and the topography of the areas. **Results** GIS mapping indicated five high prevalence areas of CKD-U. Communities who consumed water from natural springs showed a low prevalence of the disease. GPS mapping showed that most of the affected villages were located below the reservoirs and canals with stagnant irrigated water. **Conclusion** Epidemiological data on geographical distribution infers that while older foci of CKD-U are persisting, there is an emergence of new foci with time. The location of the affected villages below the level of the reservoirs/canals may indicate the possibility of draining of irrigated water to the shallow wells of the households, which is the source of drinking water.

Glyphosate, Hard Water and Nephrotoxic Metals: Are They the Culprits Behind the Epidemic of Chronic Kidney Disease of Unknown Etiology in Sri Lanka?
Jayasumana C, Gunatilake S, Senanayake P. Int J Environ Res Public Health. 2014;11(2):2125–47.

The current chronic kidney disease epidemic, the major health issue in the rice paddy farming areas in Sri Lanka has been the subject of many scientific and political debates over the last decade. Although there is no agreement among scientists about the etiology of the disease, a majority of them has concluded that this is a toxic nephropathy. None of the hypotheses put forward so far could explain coherently the totality of clinical, biochemical, histopathological findings, and the unique geographical distribution of the disease and its appearance in the mid-1990s. A strong association between the consumption of hard water and the occurrence of this special kidney disease has been observed, but the relationship has not been explained consistently. Here, we have hypothesized the association of using glyphosate, the most widely used herbicide in the disease endemic area and its unique metal chelating properties. The possible role played by glyphosate-metal complexes in this epidemic has not been given any serious consideration by investigators for the last two decades. Furthermore, it may explain similar kidney disease epidemics observed in Andra Pradesh (India) and Central America. Although glyphosate alone does not cause an epidemic of chronic kidney disease, it seems to have acquired the ability to destroy the renal tissues of thousands of farmers when it forms complexes with a localized geo environmental factor (hardness) and nephrotoxic metals.

Histopathological Characterization of Chronic Kidney Disease of Nontraditional Etiology in Salvadoran Agricultural Communities. López L, et al. MEDICC Rev. 2014 Apr;16(2). Submitted.

International Society of Nephrology's Perspective on the Emergence of Chronic Kidney Diseases of Unknown/Undetermined Etiology. Remuzzi G, Perico N. MEDICC Rev. 2014 Apr;16(2). Submitted.

Mycotoxin detection in urine samples from patients with chronic kidney disease of uncertain etiology in Sri Lanka. Desalegn B, Nanayakkara S, Harada KH, Hitomi T, Chandrajith R, Karunaratne U, et al. Bull Environ Contam Toxicol. 2011 Jul;87(1):6–10.

This was a screening study that aimed to determine the presence of nephrotoxic mycotoxins in urine samples from patients with chronic kidney disease of uncertain etiology in the North Central Province of Sri Lanka. The percentage detection of aflatoxins, ochratoxins and fumonisins in 31 patients were 61.29%, 93.5% and 19.4%, respectively. Geometric means of urinary aflatoxins and ochratoxins were 30.93 creatinine and 34.62 ng/g creatinine in chronic kidney disease of uncertain etiology stage 1-2 patients and 84.12 ng/g creatinine and 63.52 ng/g creatinine in unaffected relatives of patients. In chronic kidney disease of uncertain etiology stage 3-5 patients, geometric means of urinary aflatoxins and ochratoxins were 10.40 and 17.08 ng/g creatinine, respectively. Non-affected relatives of patients (n = 6) had comparable levels of these mycotoxins, but healthy Japanese individuals (n = 4) had lower levels than in Sri Lanka. The higher detection rate of urinary ochratoxins in Sri Lankans indicates that exposure is common in the region.

Nicaragua revisited: evidence of lower prevalence of chronic kidney disease in a high-altitude, coffee-growing village. Laux TS, Bert PJ, Barreto GM, González M, Unruh M, Aragón A, et al. J Nephrol. 2012 Jul–Aug;25(4):533–40.

Background Chronic kidney disease (CKD) is found at epidemic levels in certain populations of the Pacific Coast in northwestern Nicaragua especially in younger men. There are knowledge gaps concerning CKD's prevalence in regions at higher altitudes. **Methods** A cross-sectional study of adults between the ages of 20 and 60 years in 1 coffee-growing village in Nicaragua located at 1,000 m above sea level (MASL) altitude was performed. Predictors included participant sex, age, occupation, conventional CKD risk factors and other

factors associated with CKD suggested by previous surveys in Central America. Outcomes included serum creatinine (SCr) values >1.2 mg/dL for men and >0.9 mg/dL for women, estimated glomerular filtration rate (GFR) <60 ml/min per 1.73 m2, dipstick proteinuria stratified as microalbuminuria (30-300 mg/dL) and macroalbuminuria (>300 mg/dL), hypertension and body mass index. **Results** Of 324 eligible participants, 293 were interviewed (90.4%), and 267 of those received the physical exam (82.4% overall). Of the sample, 45% were men. Prevalence rate of estimated GFR <60 ml/min per 1.73 m2 was 0 for men (0%) and 2 for women (1.4%). The prevalence of at least microalbuminuria was significantly higher among men compared with women (27.5% vs. 21.4%, respectively; p=0.02). **Conclusions** The CKD prevalence in this village is comparable to a previously studied Nicaraguan coffee-farming region and much lower than previously screened portions of northwestern Nicaragua. There is heterogeneity in CKD prevalence across Nicaragua. At this time, screenings should target individuals living in previously identified, higher risk regions. More work is needed to understand determinants of CKD in this resource-poor nation.

Overview of the CKDu Epidemics in Central America: Current Hypothesis. McClean M, Ramirez O, Kangsen M, Laws R, Weiner D, Kaufman J, et al. Environ Health. 2013 Aug 19–23.

Chronic kidney disease of unknown etiology (CKDu) has emerged as a major public health problem in Central American. In high- and middle-income countries, CKD is primarily caused by diabetes and hypertension and is rare among adults under the age of 60. However, in Central America, diabetes and hypertension appear to play at most a marginal role and the disease affects a much younger demographic. Although data suggest an excess of disease for at least 20 years, the epidemic has received limited attention in the broader medical and public health community. The main objective of this presentation is to describe the epidemiologic characteristics of CKDu in Central America, provide the basis for subsequent presentations on research into possible causes of the disease, and similar CKDu in Southern India. The excess of CKDu in Central America is most apparent in El Salvador and Nicaragua but seems to extend across Central America and is especially concentrated in the lowlands along the Pacific coast. Men seem to be disproportionately affected, with elevated serum creatinine levels often noted in the third or fourth decade of life. Significant proteinuria is uncommon, which supports the growing evidence that the clinical profile is most consistent with tubulointerstitial disease and not glomerular disease. The etiology of CKDu remains unknown but is likely multifactorial, potentially involving a combination of causal and susceptibility factors. To date, causal hypotheses include: volume depletion and occupational exposure to heat; environmental and/or occupational expos