Reports on MeN/CKDu/CKDnT/CINAC publications presented in chronological order, i.e. when presented/published. Review papers are presented at the end of each year.

I’ve attempted to make this presentation as comprehensive as possible. I’ve read most of the cited reports thoroughly and I have subsequently made a short summary. Often – but not always – based on the abstract. Sometimes specific comments are given.

After the chronological presentation there are a few paragraphs with citations of other reports that may be pertinent, a discussion on how to interpret p-creatinine (and cystatin C) when attempting to identify changes in the glomerular filtration rate (GFR), the key renal function variable, and finally a graph on the prevalence of different levels of CKD (I to V) in a ‘normal population’. This may be useful for comparisons.

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2002
Trabanino RG, et al 2002. Possibly the first publications on the CKDu epidemic in Central America. A hospital study of 205 new dialysis patients 1999–2000 in El Salvador. For 135 of these, the cause kidney failure was unknown; it was not associated with diabetes, hypertension, primary glomerular diseases or obstructive uropathy. Patients were predominantly men (87%) had average of 51 where 63% had worked in agriculture and 73% had been exposed to agrochemicals. The authors suggested exposure to such toxic chemicals as a possible causal factor [1].

2005
Gracia-Trabanino et al 2005 examined 291 men from the coastlands of El Salvador and found a high prevalence of previously undiagnosed chronic kidney disease (CKD) (13%) having a mean creatinine of 2.6 mg/dl. It was noted that only one third (38%) of the patients with CKD had diabetes or hypertension, while the remaining did not appear to have a clear-cut cause for CKD. Farmer living, pesticides exposure and alcohol consumption were found to be very common characteristics in both populations and were not associated to the presence of proteinuria [2].

2006
Overview/review/discussion paper: Cuadra et al 2006 at a conference on Work and health in Central America, in Leon Nicaragua summarizes information available on CKD in Central America. Only limited data were available on incidence of CKD at that time, and cross-sectional results from population health screening programmes or results from occupational health examinations largely missing. However, data on mortality from chronic kidney disease in Nicaragua showed an increase from 1992 to 2002 from 4 to 10 per 100,000 inhabitants and year and remarkable differences between different regions with rates up to 35 per 100,000 inhabitants and year in Leon and Chinandega close to the pacific. It was concluded at this meeting that serious problems with chronic kidney disease exist in the area and that research on incidence, prevalence and risk factors for CKD should urgently be examined [3].
2007

Wanigasuriya et al 2007 reported that Chronic renal failure (CRF) is emerging as a major health problem in Sri Lanka. To examine risk factors 138 patients with CKD of unknown aetiology were recruited randomly from among patients at Anuradhapura Hospital (n = 136 males and n = 47 females). Patients with a serum creatinine concentration greater than 2 mg/dl with no obvious underlying cause were considered as cases. A control group of 200 subjects (n = 139 males and n = 61 females) in the age group 36—67 years, at the same hospital were selected as controls. The majority of the patients were farmers or were actively involved in farming activities (86 and 62% of males and females, respectively). Among the males, being a farmer, having used pesticides, drinking water from the well in the field, having a family history of renal dysfunction, taking Ayurvedic treatment (Hindu traditional medicine) and a past history of snake bite were more common among patients with CRF compared with controls. Although initial analysis indicated that being a farmer and use of pesticides were associated with CRF, in the multivariate model, exposure to pesticides did not impact on the development of CRF [4].

2009

Athuraliya et al 2009 in a letter to Ceylon Medical Journal that CKD of unknown aetiology was common in certain areas of Central Sri Lanka. It was noted to affect young males, from low socio-economic, paddy farming communities. Mild proteinuria (<1 gram/24 hours) and bilateral echogenic small kidneys were typical findings. Urine examination did not show evidence of high inflammatory activity and hypertension was not a common feature [5].

2010

Torres et al 2010 gave the first cross-sectional report published in an international scientific journal and revealed that an increased prevalence of CKD in certain areas of the Mesoamerica’s. In a survey more than 1300 persons from five villages of North-western Nicaragua were invited to take part in a health examination. 1,096 persons participated and provided blood and urine for analysis; a mining/subsistence farming, a banana/sugarcane, a fishing, a service and a coffee village type. In the mining/subsistence farming and in the fishing village the prevalence of elevated p-creatinine (>1.2 mg/dl) was high among men, 26% and 22% respectively, whereas it was intermediate (13%) in the fishing village and low in the service and coffee village. The pattern was similar for women, but at a lower level. An analysis of the prevalence of eGFR<60 ml/min per 1.73 m² as calculated using the MDRD formula showed a similar pattern. Proteinuria, measured by paper strip, was recorded in about one third of those with eGFR<60 ml/min per 1.73 m². It was noted the high CKD prevalent villages were located close the coast and at a low altitude and it was suggested that heavy workload in a hot climate leading to repeated dehydration may be one explanation. [6]

Sanoff et al 2010 also report from north western Nicaragua. Blood samples were obtained from 997 individuals and eGFR calculated from (using the MDRD formula) from analysis of plasma creatinine. 12.4% were identified as having an eGFR<60 ml/min per 1.73 m². In a case-control approach various exposure and demographic factors were compared with those having an eGFR>60 ml/min per 1.73 m². In a multivariable analysis age, male gender, low body mass, agricultural field work, several other types of occupations but not exposure to pesticides. Reported consumption of ‘lija’ which a type of locally brewed liquor and increasing amounts water consumed daily also comprised risk factors. It was suggested that high consumption of lija and/or contaminated water may cause CKD. However it is evident that high consumption of water, and fluids, may also be a proxy for heat exposure [7].

2011

O’Donnell et al 2011 report from a cross-sectional study in Quezalguaque, a municipality in County of Leon at the pacific coast in Nicaragua. 771 participated in a health exam including measurements of serum creatinine and eGFR was calculated from the MDRD formula. The prevalence of lowered eGFR
(eGFR<60 ml/min per 1.73 m², CKD stage 3 to 5) was overall high (12.7%) but increased markedly with age and was almost twice as high in men compared with women. In men aged 57 or older the prevalence of CKD stage 3, and 4 to 5 was 26% and 26% respectively (>3 53%). Figure 1, from this publication, present the prevalence of lowered eGFR in different age-groups of examined men in Leon compared to NHANES figures from the US population. Most of the ‘cases’ with low eGFR (<60 ml/min per 1.73 m²) did not display proteinuria (52%) or ‘trace’ (20%) and as assessed by a paper strip indicator. 21% was classified as >1+ on the paper strip indicator. There were no associations with well-known risk factors for CKD such as hypertension or diabetes [8].

Athuraliya et al 2011 provide more specific information on individuals with CKD in Sri Lanka. Screening for proteinuria was done in three areas; Medawachchiya, Yatunuwara and Hambantota. Altogether 6,153 were screened and 264 were found to have proteinuria. The prevalence of diabetes and long-standing hypertension were strikingly lower among the patients from Medawachchiya when compared with those from the other two study sites and the percentage of patients with CKD of uncertain aetiology was considerably higher (84%) in this area. Further examination of the patients with proteinuria from Medawachchiya revealed that 65% of the men and 54% of the women had an eGFR<60 ml/min per 1.73 m². The proteinuria in most of the cases were of relatively low degree and few had hypertension. 26 of 109 patients from Medawachchiya with proteinuria underwent a renal biopsy. The light microscopic findings were indicative of tubulointerstitial disease, whereas the immunofluorescence tests for immune-mediated kidney injury, IgG, IgM, IgA, and Complement 3, were negative. A toxic aetiology was hypothesized, affecting vulnerable groups of people in Medawachchiya which is a relatively poor farming area where people are more prone to become exposed chronic dehydration and environmental pollutants than other populations of Sri Lanka [9].

Orantes et al 2011 describe CKD and associated risk factors in the Bajo Lempa region of El Salvador. 775 persons (343 men) were examined. eGFR was calculated form serum creatinine using the MDRD formula. The prevalence of eGFR<60 ml/min per 1.73 m² was 17% in men and 4% in women. Aetiology was neither diabetes, obesity, nor hypertension but considered to be ‘unknown’ in most of the cases. However there were clear associations with agricultural work [10].

Overview/review/discussion paper: At World Congress of Nephrology 2011 in Vancouver, organized by the International Society of Nephrology (ISN) and the Canadian Society of Nephrology (CSN), Professor Correa-Rotter in a talk draw attention to the recently reported occurrence of lowered renal function among sugar cane workers in Central America. The name Mesoamerican Nephropathy was suggested due to similarities with another infamous kidney disease, Balkan Nephropathy, affecting inhabitants living along to the Danube river in southern Europe. For decades the cause of the Balkan Nephropathy was elusive but eventually it has convincingly been shown that Balkan Nephropathy is associated with the consumption of food containing aristolochic acid (AA) and the CKD is now better termed aristolochic acid nephropathy (AAN) [11]. In particular as also people living elsewhere may develop AAN after food, or tea, containing (AA) [12].

Chandrajith et al 2011 from Sri Lanka called attention to a high prevalence of CKD of unknown cause in certain areas of the country, in particular the north central dry zone. It was suggested that genetic predisposition and some or several environmental factors are involved in the pathogenesis [13].

2012

Nanayakkara et al 2012 give a detailed presentation on the morphological changes seen in 57 renal biopsies obtained patients with CKD of unknown aetiology examined at Anuradhapura General Hospital in Central of Sri Lanka. Frequent global sclerosis, ischemic-type obsolescence, and wrinkled and collapsed glomerular tufts were suggestive of ischemia of glomeruli. Glomerular enlargement was observed in 21 renal biopsy specimens (37%), being the second most common lesion in glomeruli. Typical FSGS lesions was observed in two specimens with non-nephrotic range of proteinuria.

In contrast to the frequently observed sclerotic lesions, no specimen showed endocapillary, extracapillary, or mesangial cell proliferation typical chronic glomerulonephritis and diabetic
glomerulosclerosis. Tubulointerstitial lesions were also seen with interstitial fibrosis being the most prominent observation and less of mononuclear cell interstitial inflammation. Arteriolar hyaline thickening score and fibrous intimal thickening was mild to moderate. This study concludes that tubulointerstitial damage is the major pathological lesion in CKDu in Sri Lanka, albeit the morphological changes that are described emphasize the glomerular lesions. It was suggested that exposure(s) to an environmental pathogen(s) should be systematically investigated to elucidate CKD of unknown cause in Central Sri Lanka [14].

Peraza et al 2012. Performed a cross-sectional study in five populations of El Salvador; Two sugarcane production communities close to the coast from where a high prevalence of CKD had been noted, and three additional villages from where there was no previous information on CKD. Altogether 664 persons were examined with measurements of blood pressure, serum creatinine and urinary paper test strips. Occupational exposure and some basic information of lifestyle and medical history were also obtained. It was possible to divide the examined population to five groups; rural coastal sugarcane, semirural coastal sugarcane, high-altitude sugarcane, coffee and urban. Significant differences in the prevalence of lowered eGFR, or elevated s-creatinine, was observed. In particular men in the two coastal sugarcane communities often displayed elevated s-creatinine (>1.2 mg/dl). The prevalence of eGFR<60 ml/min per 1.73 m² among men was 19% and 18%, whereas the prevalence of low eGFR in the high-altitude sugarcane, coffee and urban population was below 2%. In a multivariate logistic regression analysis residence coastal communities having a hot climate came out as the strongest predictor; 3.1 (CI 2.0-5.0) for each 10 year period. The prevalence of elevated s-creatinine increased with increasing number of years of work in the coastal sugarcane or cotton plantations. In spite of a high occurrence of lowered eGFR few had proteinuria; 3% of the men with eGFR >60 ml/min per 1.73 m² and 14% of those with eGFR below this level. The overall conclusion from this study was that long-term exposure to heat in connection hard physical work comprises a major risk factor for developing CKD in the area [15].

Laux et al 2012 conducted a cross-sectional study on the renal function in 267 (147 women) individuals aged 20 to 60 in a coffee-growing village in north-central Nicaragua, located 1000 meters above the sea level where the climate is less hot as compared areas close to the pacific coast. eGFR was calculated from plasma creatinine and, in contrast, to farming villages at the pacific coast less than 1% (0.7%) had an eGFR < 60 ml/min per 1.73m². Macroalbuminuria, as assessed by a paper indicator test strip, was seen in 5% of the men and 2% of women. It was noted that 92% of the men reported ‘high levels of working with pesticides’. This report thus provide support for the notion that heat exposure rather than pesticides are involved in the causative pathway of CKDu (or MeN) [16].

Senevirathna et al 2012 examined risk factors associated with mortality in 143 patients with chronic kidney disease of uncertain aetiology Sri Lanka. Eight out of 45 patients (18% aged under 65 and with eGFR below 60 ml/min per 1.73m²) 2003 had died within two years. Out of nine aged over 65 having an eGFR < 60 ml/min per 1.73m² three (33%) had died. High blood pressure was a risk factor for disease progression and death in this cohort [17].

**Overview/review/discussion paper:** Brooks et al 2012 in in an editorial in AJKD called attention to epidemic of CKD in Central America and mentioned that it ‘results in many thousands of deaths’ by refereeing to national statistics in Nicaragua and El Salvador. Points out occupational heat strain as one putative cause [18].

Funakoshi et al EHP 2012. Cross-sectional examination of prevalence of CKD in reaction to reported intake of alcohol (drinks/day) in 9,196 Japanese men (mean age 58). Negative associations were observed between reported alcohol consumption and prevalence of CKD III or higher [19].

2013

Jayasumana et al 2013 [20] analysed the arsenic concentration in urine from clinically diagnosed CKDu patients (n=125) and non-CKDu persons (n=180) in Sri Lanka. 68% of CKDu patients and 28% of the controls had urine arsenic levels above 21 μg/g creatinine and it was suggested that arsenic exposure from agrochemicals might be involved in the pathogenies of CKDu. However, albeit inorganic arsenic is severely toxic and may cause several types of systemic toxicity kidney has rarely
been reported [21]. Furthermore, monitoring of exposure to the toxic form of arsenic (i.e. inorganic arsenic) is complicated by the fact that organic forms of non-toxic arsenic is common in several forms of seafood (such as shrimps and shellfish). Consumption of certain types of common seafood may thus increase the urinary excretion of arsenic considerably. In order to differentiate between exposures to inorganic, or organic ‘non-toxic’ arsenic speciation of arsenic in urine is needed, and this was not done in this study, merely total arsenic was measured. Possibly the type of food varied between CKDu patient and controls.

Ramirez-Rubio (2013) and a team from Boston University School of Public Health made a semi-structured interview with 10 physicians and 9 pharmacists in North-western Nicaragua which has a high prevalence of chronic kidney disease (CKD) of unknown cause. The interviews were performed 2010. Health professionals perceived CKD as a serious and increasing problem in the region, primarily affecting young men working as manual labourers. 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 a set of symptoms referred to locally as “chistata,” characterized by painful urination and often accompanied by “kidney” and/or back pain. The health professionals indicated that reluctance among workers to hydrate might be influenced by perceptions of water contamination. Symptoms often were treated with self-medication using non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and antibiotics. Albeit the diagnosis of urinary tract infection was sometimes set ant treated with antibiotics this diagnose war usually was not based on microbial culture. Likewise the incidence renal stones was not considered be unusually high or frequently diagnosed. Despite the media attention given to the potential role of agrichemicals in causing CKD, physicians and pharmacists were much more likely to cite exposure to heat, physical work and dehydration as key factors responsible for the CKD development [22].

That heat exposure during sugarcane harvesting in Costa Rica has been shown. Non-participatory observation and Wet Bulb Globe Temperatures (WBGT) measurements were carried out during two typical working-week in 2012 and 2011 in Guanacaste, in north western Costa Rica. Sugarcane in this area is typically burnt the night before harvesting, and these ads to the ambient heat exposure. Already at 7:15, after a little more than one hours work, the OSHA threshold of 26.0 degrees WBGT was reached after 4 hours 30.0 degrees was often reached at which level no more than 15 minutes per hour is recommended to avoid health risks. However the sugarcane cutters typically kept on for several more hours (until noon) to get there needed income which typically is based on the amount (weight) of the cut [23].

The first detailed clinical and pathological characterization of what has been named Mesoamerican Nephropathy (MeN) was published 2013[24]. Eight male patients with CKD of unknown cause and clinically suspected MeN were examined in El Salvador. All had been working on plantations. Renal morphology examined with light microscopy, immunofluorescence and electron microscopy. A similar morphological 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-EPI eqution, low-grade albuminuria, and increased levels of tubular injury biomarkers. Hypokalemia was found in 6 of 8 patients. This observation (low potassium) in combination with glomerular changes indicative of ischemia suggested that perturbations in the renin angiotensin system due to excessive and repeated losses of salts due to excessive sweating may be involved in the pathogenies [24].

**Overview/review/discussion papers:** Wesseling et al 2013 in AJPH. A summary and call for action and further research based on the conference in Costa Rica in December 2012. Emphasize that the most affected group are sugarcane cutters, exposed to extreme ambient heat during hard physical work. Repeated episodes with dehydration with loss electrolytes and minerals with attending AKI was considered to be the leading hypothesis and pathway to cause the epidemic of CKDu in Central America. Alternative hypothesis and cofactors were also considered needing further attention; NSAID use, inorganic arsenic, and infection from leptospirosis. However based on available evidence at the
time of the meeting (December 2012) pesticides, hard water and urinary tract infections were considered unlikely causes. At the workshop it was also pointed out that heat stress-associated CKD possible is not an isolated Mesoamerican problem and that are suggestive evidence that it also occurring in Sri Lanka [25].

Lewington et al (2013) in KI make an attempt to raise the awareness that acute kidney injury (AKI) is a major global health problem resulting in millions of deaths per year on a global basis. If not prevented, or treated, properly a large proportion of the incident AKI may progress to CKD and ESRD. Proper hydration, and rehydration, and avoidance of nephrotoxic drugs are key elements for prevention [26].

2014

Rosa-Diez et al 2014 present data on the prevalence of renal replacement therapy (RRT) in twenty Latin America countries. The overall prevalence of RRT is rapidly increasing and was 660 per million in 2011. El Salvador and Nicaragua, which have areas with many cases of CKD from MeN, have the lowest RRT rates; 28 and 11 per million. These low prevalence figures are most probably due to insufficient allocation of resources as there was an almost linear and highly significant correlation between each country’s gross national income and prevalence of RRT [27].

In 2014 two medical students, Krinsky and Levine in KI, gave a personal presentation of the CKD epidemic in Nicaragua; Chronic kidney disease of unknown origin (CKDu), also known as Mesoamerican Nephropathy or Mesoamerican endemic Nephropathy. La Isla Foundation from the nickname for ‘La Isla de Víduas’ or the Island of Widows. Cite information from the area reporting that ‘at least 3000 people in Chinandega (a region in north western Nicaragua with population of around 150,000) alone has the disease. Present the almost unsurmountable difficulties to provide peritoneal dialysis to patients with end stage renal disease due to poverty, insufficient training and medical support and in particular poor hygienic facilities at the homes of affected individuals [28].

Raines et al 2014 report from one of the most affected townships in Nicaragua; community near the town of Chichigalpa. Participants were recruited using door-to-door canvassing in May–June 2012. All eligible household members were invited to a single study visit at a central location for interview on medical history and various environmental and occupational exposures and physical and biochemical measures which included urine paper strip and analysis of serum creatinine and calculation of eGFR using the CKD-EPI formula. 424 people (166 men) participated. Mean age was 32 for men and 35 for women. Prevalence of eGFR <60 mL/min/1.73 m² was 42% among men 9.8% in women. Among participants with GFR <60 mL/min/1.73 m², 44% had proteinuria ≥30mg/dL and only 7 participants (9%) had proteinuria ≥300 mg/dL. A subset of the participants formed the base for a case-control analysis to assess risk factors for reduced GFR, with cases defined as individuals with a single GFR calculation <60 mL/min/1.73 m² and controls defined by an eGFR >90 mL/min/1.73 m². Hypertension was more prevalent among cases than controls although overall prevalence of hypertension was only 8.6%. Prevalence of HbA1c >6.5% was 3.7% in case group and 3.2% in control group (p = 0.88. NSAID use was common (>70% in both cases and controls and there was no significant difference between cases and controls (p = 0.44). Aside from age and male sex, the strongest independent association observed was between reduced GFR and lifetime hours cutting sugarcane, particularly during the dry season. In models adjusted for total hours cutting sugarcane during the dry season, a history of high bolis consumption (a sugary rehydration packet)(OR 1.39, 95% CI 0.99–1.95) and inhaling pesticides (OR 2.61, 95% CI 0.99–6.90) were close to significant [29].

VanDervort et al (2014) in an exploratory ecological study in El Salvador analysed unspecified CKD (unCKD) and non-diabetic ESRD (nESRD) hospital admissions. 16,384 and 8,342 respectively in 242 municipalities. Admission rates for CKD was calculated and related to environmental factors and type of production in these municipalities. The areas of highest unspecified CKD admission rates were located in the south-western municipalities of La Paz Department. This area is the region of highest ambient temperatures (33–36 ºC) in El Salvador. Percent area of sugarcane cultivation produced the
greatest bivariate regressions. However, when models where made more complex multivariate and sophisticated association with heat become less evident [30].

Orantes et al 2014 report from a population screening study in El Salvador. 2388 individuals in three agricultural communities were examined: Bajo Lempa, Guayapa Abajo and Las Brisas (976 men. The prevalence of CKD was (eGFR <60 mL/min/1.73 m²) was high in all three villages, 6.8% in woman and 17% in men and increased with age. At age >60 57% of men and 28% of women had eGFR below 60 mL/min/1.73 m². Few displayed proteinuria. As in other cross-sectional studies neither hypertension nor diabetes or obesity was particularly high in these communities, but the prevalence lowered eGFR was twice as common among in kidney function male agricultural works compared to non-agricultural workers. Contact with of agrochemicals was common among men and reported by 54 of the men and 17% of women. Use of NSAIDs was overall common and similar in both sexes (84% in men, 84.3% in women. The others were not able to pinpoint any specific type of exposure that could explain the high prevalence of CKD in the examined populations but that 'poor working conditions, and contact with agrochemicals' are involved [31].

Herrera el al 2014 present clinical characteristics from 46 participants in the El Salvador screening programme reported by Orantes et al (2014) who were aged between 18-59 and had an eGFR<60 mL/min/1.73 m². Overall the patients characterized by poverty were the leading social determinant observed. Risk factor Prevalence of various conditions and exposures where as follows; exposure to agrochemicals (95.7%), agricultural work (78%), male sex (78%), profuse sweating during work (76.3%), malaria (44%), NSAID use (41%), hypertension (37%), diabetes (4%). General symptoms included: arthralgia (54.3%), asthenia (52%), cramps (46%), and fainting (30%). Renal symptoms included: nycturia (65%), and dysuria (39.1%). Markers of renal damage where often abnormal in this group of selected patient with low eGFR; macroalbuminuria (80%), elevated β2 microglobulin (78%), and NGAL (26%). These data are however somewhat difficult to interpret as only 26 individuals were reported to have macroalbuminuria in the screening report and cut-of levels for β2 microglobulin and NGAL are not given. Analysis of plasma showed that metabolic alkalosis (46%), hyponatremia (48%), hypocalcaemia (39%), hypokalemia (30%), and hypomagnesemia (20%) was common in this group [32].

López-Marín et al 2014 performed renal biopsies of the patient’s characterized by Herrera et al 2014 in El Salvador. The main findings were interstitial fibrosis and tubular atrophy with or without inflammatory monocyte infiltration. In addition, generalized glomerulosclerosis, increased glomerular size, collapse of some glomerular tufts, and lesions of extraglomerular blood vessels (such as intimal proliferation and thickening and vacuolization of the tunica media) were observed. Overall these observations are well compatible with those presented by Wijkström et al (2013) albeit the authors of this report concludes that the renal biopsies are more consistent with tubulointerstitial nephritis accompanied by glomerular damage and concluded that toxic environmental or other occupational exposures, chronic ischemia from dehydration, or nephrotoxic medications, are all compatible with the histopathological findings [33].

Vela et al 2014 present another descriptive cross-sectional study from two El Salvadoran farming communities; Dimas Rodríguez (El Paisnal municipality) and El Jícaro (San Agustín municipality) facing the Pacific with an alarming high prevalence of CKD: A total of 223 persons of both sexes were studied. Overall prevalence of chronic kidney disease was 16.1% (men 10.9%; women 21%). It noteworthy that CKD was more common in women than in men in this study. Most of the examined reported agrochemical occupation and contacts with agrochemicals. [34]

Ordunez et al (2014) presents data on the age standardized mortality rate due to chronic kidney disease in Nicaragua and El Salvador compared to other countries in the region. The age standardized mortality rate due to chronic kidney diseases (coded as N18 (CKD-N18) by the 2010 International Classification of Diseases) which is notably higher for men and women in Nicaragua and El Salvador compared to other countries in the region, and rapidly increasing. In men aged 50-54 the mortality rate in CKD in Nicaragua and El Salvador 2000-2009 was about 110/100,000 population compared to less than 40/100,000 population in countries such as Panama, Cuba and Costa Rica. Lack of dialysis
facilities in Nicaragua and El Salvador can hardly explain these remarkable differences in CKD mortality: The data really confirms that a fatal endemic of CKD is occurring in these two countries [35].

Santos et al 2014 examined 28 healthy non-African Brazilian workers engaged in sugar cane harvesting during 2009. Blood and urine samples were collected before starting harvest, and before and after a workday in the last month of the harvesting season. Although there were no systematic change in p-creatinine at start of work the harvesting season and a morning sample later, p-creatinine at the end the workday (taken at the end of the harvest season) had increased in all men (average 21 umol/l), and eGFR dropped on average about 20 ml/min per 1.73 m2 and Five of the 28 examined men (18%) displayed acute kidney injury as was diagnosed by the p-creatinine increase. During the harvesting season the men worked from 7 to 16 hours, six days a week cutting in the order of 10 tons of burnt sugarcane per day in a high ambient temperature. Several of the workers experienced frequent cramps during the cutting season and measurement of urine osmolarity (average 890 mOsm/l) revealed that significant dehydration occurred during the cutting. White blood cells also increased significantly during the heavy work, and there were significant positive correlations between p-creatinine on the one hand and changes in haematocrit, or serum albumin, on the other [36]. In context of rapidly increasing p-creatinine after a workday seen at the end of the harvest is worth noting that GFR need to drop rather dramatically to result in an increase of the p-creatinine concentration of 20 umol/l within 8 hours (50%). It may be speculated that the increase in p-creatinine is a result of creatinine release from muscle cells rather than change in GFR.

Roncal Jimenez et al 2014 in an animal model have elucidated a possible mechanism for heat and dehydration induced nephrotoxicity involving activation of renal fructokinase. Wild-type and fructokinase deficient mice were subjected to recurrent heat-induced dehydration. This was achieved by placing mice in heated chambers for a total of 3.5 h per day, for 5 days per week, for a total of 5 weeks. The first major finding was that the mice that were severely dehydrated (losing on average 15% of their body weight), during the day and had delayed rehydration activated the aldose reductase pathway in their kidneys, and this was associated with the development of renal injury, as noted by an increase in urinary neutrophil gelatinase-associated lipocalin, an increase in serum creatinine, proximal tubular injury by biopsy, an increase in renal MCP-1 and macrophage infiltration, and early renal fibrosis. This was associated with activation of the polyol pathway, with increased renal cortical sorbitol and fructose levels. Mice that were exposed to the same heat but who hydrated during the day were protected. Interestingly mice lacking fructokinase were protected from renal injury despite similar degrees of dehydration. These experimental studies may have practical consequences also on the type of rehydration that is provided and recommended. Many of the sugar cane cutters hydrate themselves with fructose-rich juices or beverages that might compound the problem with dehydration as the acute renal injury might be potentiated by fructose provided in the drinks [37].

Wesseling et al 2014 examined the geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica. Standardized mortality ratios (SMRs) were compared for three time periods between provinces and counties. In the Guanacaste province at the NW Pacific coast of Costa Rica, where MeN is known to occur, the CKD mortality increased from the mid-1970s. Age-standardised rates per 100,000 in men aged over 29 increased from 5.8 in the early seventies to 75.0 in 2007-2012, compared to 5.9 to 16.2 in the rest of Costa Rica. For women, rates increased from 4.5 to 20.7 in Guanacaste versus 4.2 to 9.7 in the rest of the country [38].

42 male patients older with confirmed CKDu were interviewed about how they used pesticides in three communities of Bajo Lempa region, El Salvador [39]. Interviewed did not use appropriate personal protective equipment; hazardous pesticides were often misused, 95% of interviewed mixed different types pesticides and 63% dumped empty pesticide containers in the fields. There was inadequate legislation and a poor law enforcement to prevent the misuse of pesticides in El Salvador at the time of this report. Very similar results were also reported later [40] but included also some environmental measurements of cadmium and arsenic.
Overview/review/discussion papers: At the first international MeN meeting it was concluded. ‘There is an epidemic of chronic kidney disease of unknown aetiology (CKDu) in several parts of Mesoamerica. This public health problem is of such magnitude and severity that urgent, exhaustive 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’.

The consensus of the workshop was that ‘the strongest causal hypothesis for the epidemic is repeated episodes of heat stress and dehydration during heavy work in hot climates. Co-factors to consider interacting with heat stress or influencing the progression of CKDu, include excess use of nonsteroidal anti-inflammatory drugs (NSAIDs) and fructose consumption in rehydration fluids. Contributing factors for the epidemic could include inorganic arsenic, leptospirosis, pesticides, or hard water. Interventions to reduce heat stress and improve hydration with controlled trials are recommended.’ [41].

Correa-Rotter et al (2014) provide a more in depth presentation from the first international MeN meeting in Costa Rica, present epidemiologic studies on CKD in Central America and discuss pros and cons for a number of suggested causative factors including: Aristolochic Acid and Mycotoxins, Heavy Metals, Agrochemicals, Leptospirosis and Other Infectious Causes, Alcohol Drinks Containing Toxins, Nonsteroidal Agents and Other Nephrotoxic Drugs, Recurrent Dehydration/Volume Depletion, Fructose, Hypokalemia and Hyperuricemia, and Social Determinants.

Heat stress, dehydration end volume depletion was the only potential causes given ‘high priority’ and activation of the fructokinase pathway was suggested as a potential mechanism for dehydration associated CKD. The use of nephrotoxic medications was considered a possible cofactor, in particular the concomitant use of NSAID and heat dehydration. Other exposures were given low or medium priority. Prevention and treatment were also touched upon. The best-known prevention is possibly to provide adequate hydration and limit exposure of workers to heat. Working in the early morning hours before the temperature gets excessive may be of benefit. Increased drinking of water is recommended to minimize the effects of excessive sweating, and avoidance of NSAIDs is highly recommended. Providing appropriate sources of hydration and sanitation and allowing for reasonable working shifts accompanied by periods of rest and provision of shade are all recommended strategies for prevention. Rehydration interventions should be adequately studied for effectiveness by means of field trials. Even if pesticides eventually are found not to cause CKD, there is no doubt that any potential hazards associated with their use should be minimized, and sustainable nontoxic pest control methods should be encouraged [42].

Wernerson et al 2014 present an update on different forms of endemic nephropathies and point out that in addition to epidemiologic studies which focus on the prevalence of nephropathy in different areas and its association with different risk factors careful clinical studies, case reports and renal biopsies, are needed to fully understand and unravel the possible mechanism [43].

Robey 2014; in an editorial in KI suggest that, based on animal experiments, fructokinase deficiency and fructose metabolism may be promoting a dehydration-induced acute kidney injury to CKD [44].

Jayasumana et al 2014 in a review paper on the possible cause(s) of the ongoing epidemic of CKD affecting the population of several rice paddy farming areas of Sri Lanka suggest that the culprit is the used herbicide: glyphosate. This is the most commonly used pesticide in Sri Lanka, highly water soluble, chelating and may form complexes with metals and other constituents of hard water. Consumption of hard water has previously been related to a high incidence of CKDu in Sri Lanka. However, the evidence presented are, as yet, mainly circumstantial [45].

Almaguer et al 2014 provide a review of chronic kidney disease of unknown aetiology in agricultural communities globally, by reviewing published findings from El Salvador, Nicaragua, Costa Rica, Sri Lanka, Egypt and India. Summarizes that associations were reported with agricultural work, agrochemical exposure, dehydration, hypertension, homemade alcohol use and family history of chronic kidney disease. According to the authors there is no strong evidence for a single cause, and multiple environmental, occupational and social factors are probably involved [46].
**2015**

**Laws et al (2015)** investigated changes and job-specific differences over a 6-month sugarcane harvest season in 284 Nicaraguan sugarcane workers performing seven distinct tasks as; cane cutters (n=51), seeders (n=36), seed cutters (n=19), agrochemical applicators (n=29), irrigators (n=49), drivers (n=41) and factory workers (n=59). eGFR (CKD-EPI equation) varied by job and decreased during the harvest in all groups considered to be exposed to ‘heat stress’ groups and significantly so in seed cutters (-4.5 ml/min/1.73 m²) and irrigators (-4.9 ml/min/1.73 m²) but was not seen in drivers and factory workers not exposed to ‘heat stress’. The number of years employed at the company was negatively associated with eGFR. Fewer than 5% of workers had albumin-to-creatinine ratio (ACR) >30 mg/g. cane cutters (n=51), seeders (n=36), seed cutters (n=19), agrochemical applicators (n=29), irrigators (n=49), drivers (n=41) and factory workers (n=59). eGFR (CKD-EPI equation) varied by job and decreased during the harvest in all groups considered to be exposed to ‘heat stress’ groups and significantly so in seed cutters (-4.5 ml/min/1.73 m²) and irrigators (-4.9 ml/min/1.73 m²) but was not seen in drivers and factory workers not exposed to ‘heat stress’. One weakness in this study is that eGFR is calculated from serum creatinine and as the differences between groups and changes in serum creatinine over time are relatively small (from ~7% to ~9%) the interpretation may be confounded by variations in diet and/or intrinsic muscle composition which may well be influenced by a physically demanding work, such as cane cutting. Another methodological problem is the circumstance that workers with elevated creatinine already at the start of the season where not hired. Thus the examined group to some extent comprise a selection of healthy individuals.
Orantes Navarro et al 2015. In a cross-sectional study 2009 - 2011 examined 1,412 women aged ≥ 18 years in three disadvantaged populations of **El Salvador**: Bajo Lempa (Usulután Department), Guayapa Abajo (Ahuachapán Department), and Las Brisas (San Miguel Department). eGFR was calculated from the CKD-EPI formula. Prevalence of CKD (eGFR < 60 ml/min/1.73 m²) was 13.9%. 5.7% had microalbuminuria (30 - 300 mg/L) and 0.8% macroalbuminuria (> 300 mg/L). Information of various risk factors were reported and 31% reported contact with agrochemicals. The study confirms that CKDu is a major health problem in poor populations of El Salvador, and also among women. Unfortunately, exposure to heat and water and salt depletion was not reported [51].

Herrera Valdés R et al 2015 undertook a thorough exam, including renal biopsies from 10 of the screened women. 9 of them had U-albumin exceeding < 0.3 g/mol creatinine and 7 of the eGFR > 60 ml/min/1.73 m². Histopathological findings were rather non-specific and included interstitial fibrosis and glomerulomegaly. Due to the selection of the examined patients (from a large screening programme) and the high prevalence of albuminuria and a relatively high eGFR in most of the examined woman the results are not really comparable with other case series of CKDu or MeN [52].

Crowe et al (2015) examined the frequency of heat-related health effects among harvesters in **Costa Rica** (n = 106) exposed to occupational heat stress compared to non-harvesters (n = 63). Heat and dehydration symptoms (headache, tachycardia, muscle cramps, fever, nausea, difficulty breathing, dizziness, swelling of hands/feet, and dysuria) were experienced at least once per week significantly more frequently among harvesters. Percentages of workers reporting heat and dehydration symptoms increased in accordance with increasing heat exposure categories [53].

Laux et al (2015) analysed enrolment rates in RRT **Guatemala** and found the rates were significantly in the Southwest compared to the rest of the country and concluded that the elevated incidence had a similar geographic distribution as Nicaragua and El Salvador (higher in the high temperature and sugar cane growing regions), and that it is likely that the CKD epidemic extends throughout the Mesoamerican region [54].

Lebov et al (2015) conducted a cross-sectional study of 2275 residents in Leon, **Nicaragua**. CKD (eGFR<60 ml/min/1.73 m²) prevalence was 9.1%; twice as high for males (13.8%) than females (5.8%). Older age, rural zone, lower education level, and self-reported high blood pressure, more years of agricultural work, lija (unregulated alcohol) consumption, and higher levels of daily water consumption were significantly associated, and dose-response related with. Adjusted odds ratio for low eGFR increased from 1.3, 1.7, 2.6 and 2.9 with increasing five years of work in agriculture and likewise decreasing educational level. This study provides additional support for an environmental and/or occupational cause of MeN [55].

Further support dehydration and loss of minerals being the major cause of MeN have been presented from **El Salvador** (Garcia-Trabanino et al 2015). Sugarcane cutters (N=189, aged 18–49 years, 168 of them male) from three regions in El Salvador were examined before and after shift. Cross-shift changes in markers of dehydration and renal function were examined and associations with temperature, work time, region, and fluid intake were assessed. Pre-shift glomerular filtration rate was estimated (eGFR). Pre-shift serum uric acid levels were remarkably high and pre-shift eGFR was reduced (<60 mL/min) in 23 male workers (14%). The mean work-time was 4 (1.4–11) hours. Mean workday temperature was 34–36 °C before noon, and 39–42°C at noon. The mean liquid intake during work was 0.8 L per hour. The mean urine specific gravity, urine osmolality and creatinine increased, and urinary pH decreased. Serum creatinine, uric acid and urea nitrogen increased, while chloride and potassium decreased. The changes are consistent with recurrent dehydration from strenuous work in a hot and humid environment and a pathophysiology including decreased renal blood flow, high demands on tubular reabsorption, and increased levels of uric acid [56].

Wijetunuge et al (2015) in a retrospective study of 251 renal biopsies from **Sri Lanka**. The predominant feature of stage I disease was mild and moderate interstitial fibrosis; most did not have interstitial inflammation. The typical stage II disease had moderate interstitial fibrosis with or without mild interstitial inflammation. Stage III disease had moderate and severe interstitial fibrosis, moderate interstitial inflammation, tubular atrophy and some glomerulosclerosis. Stage IV disease typically had severe interstitial fibrosis and inflammation, tubular atrophy and glomerulosclerosis [57].
Lebov et al (2015) evaluated the association between exposure to 39 specific pesticides and end-stage renal disease (ESRD) incidence in a cohort study of licensed pesticide applicators in Iowa and North Carolina. 320 ESRD cases were diagnosed among 55,580 male licensed pesticide applicators. Participants provided information on use of pesticides via self-administered questionnaires. Cox proportional hazards models, adjusted for age and state, were used to estimate associations between ESRD. A great number (<100!) statistical associations were examined and a few showed statistical significance. Positive exposure-response trends were observed for the herbicides alachlor, atrazine, metolachlor, paraquat, and pendimethalin, and the insecticide permethrin. More than one medical visit due to pesticide use (HR=2.13; 95% CI 1.17 to 3.89) and hospitalisation due to pesticide use (HR=3.05; 95% CI 1.67 to 5.58) were also significantly associated with ESRD [58].

Overview/review/discussion papers: Elinder et al (2015) in an extensive review summarizes what has been published up to the mid 2015 on Mesoamerican Nephropathy (MeN) and a similar type of CKD in Sri Lanka. An epidemic of CKD affecting agricultural workers in the Mesoamerica. At an early stage the kidney disease is characterized by a lowered glomerular filtration rate (GFR) but no, or limited, albuminuria. It mainly affects men that have been working for years with hard physical work in hot climate prone to repeated episodes of dehydration and, as result of this, repeated subclinical acute kidney injuries. Cofactors for the development of the disease, such as consumption of NSAID and large amount of fructose rich fluids, and genetic predisposition possibly exist. Severe and terminal CKD may develop. Thousands of inhabitants along the Pacific coast possibly are affected. Histopathological examination of renal biopsies shows glomerular and interstitial changes that are compatible with repeated episodes of ischemia. Reports from Sri Lanka indicate that agricultural workers in certain areas of the island may develop CKD of a similar type [59].

Another review on MeN, which is updated regularly and available on line appear in UpToDate since 2015 [60].

Measurement of arsenic, cadmium and lead in biological media from populations with CKD of unknown cause in Central America has not shown potentially toxic levels of these metals, rather levels are in the normal range. Likewise, the concentration of a series of potentially nephrotoxic metals, including arsenic, cadmium, lead and lithium has recently been measured in drinking water and urine from patients with CKDu, and individuals without CKDu in CKD endemic and non-endemic areas of Sri Lanka. Overall the concentrations were low in water as well as in urine and there was nothing indicating a causative association between exposure to metals and CKDus [61].

Likewise, Wimalawansa (2015) in a review from Sri Lanka concludes that available data do not support any so far postulated agents, chemicals, heavy metals, fluoride, salinity/ionicity, or individual agrochemical components, such as phosphate or glyphosate, as causative factors for the CKD epidemic in parts of Sri Lanka. A combination of these factors (or an unknown toxin) together with harmful behaviour and chronic dehydration may cause this disease [62].

Lunyera et al (2015) provides an overview of epidemics of CKD of uncertain etiology (CKDu) are emerging around the world, searched PubMed, Embase, Scopus and Web of Science databases to identify published studies on CKDu. 1607 articles, of which 26 met inclusion criteria. Eighteen (69%) were conducted in known CKDu-endemic countries: Sri Lanka (38%), Nicaragua (19%), and El Salvador (12%). The other studies were from India, Japan, Australia, Mexico, Sweden, Tunisia, Tanzania, and the United States. Heavy metals, heat stress, and dietary exposures were reported across all geographic regions. In south Asia, family history, agrochemical use, and heavy metal exposures were reported most frequently, whereas altitude and temperature were reported only in studies from Central America. Across all regions, CKDu was most frequently associated with a family history of CKDu, agricultural occupation, men, middle age, snake bite, and heavy metal exposure [63].

Weaver et al (2015) in an overview emphasises that CKDu appears to have a complex and possibly multifactorial cause, but exposure to metals such as cadmium, lead and arsenic to not appear to have a major role [64].
Murray et al 2015 [65] suggested that Mesoamerican nephropathy might have an infectious etiology in the Chichigalpa area, in Chinandega, Nicaragua. In this ‘hot-spot’ area interviewed patients had often experienced fever, nausea and vomiting, arthralgia, myalgia, headache, neck and back pain, weakness, and paresthesia at the onset of acute kidney disease. Rodents, particularly of Sigmodon species, in are common in the sugarcane fields where most of the patients have been working. It was hypothesized that infectious pathogens are being shed through the urine and feces of these rodents, infecting agricultural workers in sugar cane plantations. But no evidence for this theory was presented.

2016

Regional variations in prevalence the prevalence of chronic kidney disease (CKD) in Costa Rica have been analysed and reported 2019 [66]. A cohort comprised of 2657 adults born before 1946 in Costa Rica was chosen through a sampling algorithm to represent the national population of Costa Ricans >60 years of age. Participants answered questionnaire data and completed laboratory testing. The primary outcome of this study was CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m². The overall estimated prevalence of CKD for older Costa Ricans was 20% (95% CI 18.5-21.9%). In multivariable logistic regression, older age (adjusted odds ratio [aOR] 1.08 per year, was independently associated with CKD. For every 200 m above sea level of residence, subjects’ odds of CKD increased 26% (OR 1.26). There was large regional variation in adjusted CKD prevalence, highest in Limon (40%) and Guanacaste (36%) provinces. Regional and altitude effects remained robust after adjustment for socio-economic status. These provinces also display a higher mortality rate in CKD, have a high proportion of immigrants from other Central American countries, including Nicaragua, and are engaged in agricultural activities; the main crops in Guanacaste are beef, sugar cane and rice, whereas in Limon, bananas and other fruits are predominant.

Bodin and co-workers (2016) examined an intervention modelled on OSHA’s Water-Rest-Shade programme (WRS) during sugarcane cutting in El Salvador. Health data (anthropometric, blood, urine, questionnaires) were collected pre-harvest, pre-intervention, mid-intervention and at the end of harvest. Self-reported water consumption increased 25% after the intervention. Symptoms associated with heat stress and with dehydration decreased. At the same time the individual daily cut cane production increased. A WRS intervention is feasible in sugarcane fields and appears to markedly reduce the impact of the heat stress conditions for the workforce. With proper attention to work practices, production can be maintained with less impact on worker health [67].

Laux et al (2016) document the prevalence of non-traditional causes (CKDnt) among 242 hemodialysis in southwestern Guatemala. The prevalence of CKDnt appeared to be lower than in El Salvador. Nevertheless 242 total patients (including 171 non-diabetics) enrolled in hemodialysis in southwestern Guatemala, 45 (18.6% of total patients and 26.3% of non-diabetics) lacked traditional CKD risk factors [68].

A descriptive epidemiologic study on children (<18 years) in three agricultural regions with known high prevalence of chronic kidney disease of uncertain etiology: Bajo Lempa, Guayapa Abajo and Las Brisas, El Salvador has been reported [69]. Prevalence of microalbuminuria was 4%; 4.3% in girls and 3.8% in boys. eGFR, based on the Schwartz formula was higher than anticipated and the prevalence of abnormally low eGFR was only 0.1%.

Kupferman et al (2016) performed a cross-sectional family-based study among 266 members of 24 families with high chronic kidney disease (CKD) burdens in a MeN hotspot in North-western Nicaragua. Hyperuricemia was common among patients with MeN. The results suggest that rather than being solely a consequence of CKD, hyperuricemia may play a role in MeN pathogenesis, a hypothesis that deserves further study [70].

Roncal-Jamines et al (2016) argue that MeN may be a uric acid disorder. Individuals at risk for developing the disease are primarily male workers exposed to heat stress and physical exertion that predisposes to recurrent water and volume depletion, often accompanied by urinary concentration and acidification. Uric acid is generated during heat stress, in part consequent to nucleotide release from muscles. They hypothesize that working in the sugarcane fields may result in cyclic uricosuria in
which uric acid concentrations exceed solubility, leading to the formation of dihydrate urate crystals and local injury. Consistent with this hypothesis, they present pilot data documenting the common presence of urate crystals in the urine of sugarcane workers from El Salvador. High end-of-workday urinary uric acid concentrations were common in a pilot study, particularly if urine pH was corrected to 7. Hyperuricemia may induce glomerular hypertension, whereas the increased urinary uric acid may directly injure renal tubules. Thus, MeN may result from exercise and heat stress associated with dehydration-induced hyperuricemia and uricosuria. Increased hydration with water and salt, urinary alkalinization, reduction in sugary beverage intake, and inhibitors of uric acid synthesis should be tested for disease prevention [71].

Laux et al in 2016 [54] interviewed patients on hemodialysis in southwestern Guatemala who had chronic kidney disease (CKD) of non-traditional causes (CKDnt). Of 242 total patients (including 171 non-diabetics) 45 (18.6% of total patients and 26.3% of non-diabetics) lacked traditional CKD risk factors. While agricultural work history was common, only travel time greater than 30 minutes and age less than 50 years old were significantly associated with CKD in the absence of traditional risk factors.

Wesseling et al (2016) performed a cross-sectional study in Chinandega and Leon municipalities, a MeN hotspot on the Nicaraguan Pacific coast. 194 male workers aged 17-39 years: 86 sugarcane cutters, 56 construction workers, 52 small-scale farmers. Sugarcane cutters were more exposed to heat and consumed more fluid on workdays and had less obesity, lower blood sugar, lower blood pressure and a better lipid profile. Reduced eGFR occurred in 16%, 9% and 2% of sugarcane cutters, construction workers and farmers, respectively. Sugarcane cutters also more often had proteinuria and blood and leucocytes in the urine. Workers with eGFR <80 mL/min/1.73 m2 reported a higher intake of water and lower intake of sugary beverages. Serum uric acid levels related strongly and inversely to eGFR levels [72].

Wesseling et al (2016) present an important study on kidney function changes among male sugarcane cutters in Nicaragua during the harvest period. A group of male sugarcane cutters in Nicaragua (N=29, aged 17-38 at start of harvest, and then at end of harvest 5 months later. The pre-shift renal function (eGFR) decreased significantly during 9 weeks of work in the cane cutters (9%, or 10mL/min and mean urinary neutrophil gelatinase-associated lipocalin (NGAL) increased (four times). The longitudinal decrease in eGFR tended to be associated with the cross-shift increase in serum creatinine [73].

Badurdeen et al (2016) present the clinicopathological profile of a group of patients presenting with acute symptoms and renal dysfunction from CKDu endemic regions in Sri Lanka was studied. Patients' mean age, occupation, and sex ratio were 44 (9) years, 57 farmers, and male/female 55/4, respectively. Mean serum creatinine at biopsy was 143.8 (47.9) micromol/L. Elevated inflammatory markers and active urine sediment were reported. Histology was compatible with an interstitial nephritis with a mixture of acute and chronic tubulointerstitial lesions and glomerular scarring. In the natural course of an acute episode of CKDu, serum creatinine and histological activity were reduced while histological chronicity increased [74].

Dare et al (2016) investigated changes in adult renal failure mortality and its key risk factors in India. Age-standardised renal death rates were highest in the southern and eastern states, particularly among adults aged 45-69 years in 2010-13. Diabetes, hypertension, and cardiovascular disease were all significantly associated with increased renal failure deaths, with diabetes the strongest predictor-odds ratio (OR) vs control 9.2 (95% CI 6.7-12.7) in 2001-03, rising to 15.1 (12.6-18.1) in 2010-13. In the 2010-13 study population, the diabetes to non-diabetes OR was twice as large in adults born in the 1970s (25.5, 95% CI 17.6-37.1) as in those individuals born during or before the 1950s (11.7, 9.1-14.9). Renal failure is a growing cause of premature death in India. Poorly treated diabetes is the most probable reason for this increase [75].

or hypertension. Few received RRT. Patient mortality is high even with RRT. Most patients are male (9:1). Social determinants influenced the high mortality [76].

Roncal-Jimenez et al (2016) exposed rats to heat stress and recurrent dehydration. This induced functional changes (albuminuria, elevated urinary NGAL), glomerular changes (mesangiolysis, matrix expansion) and tubulointerstitial changes (fibrosis, inflammation). Addition of injection of desmopressin exacerbated the injury. Both heat stress and/or desmopressin were also associated with activation of the polyol pathway in the renal cortex, likely due to increased interstitial osmolarity [77].

Moyce et al (2016) investigated the cumulative incidence of acute kidney injury (AKI) over one work shift among agricultural workers in California. Serum creatinine was measured both before and after a work shift. In 295 agricultural workers, AKI after a summer work shift was detected in 35 participants (12%) [78].

**Overview/review/discussion papers:** Roncal-Jimenez et al (2016) in a review concludes that an epidemic of chronic kidney disease (CKD) of unknown cause has emerged along the Pacific Coast of Central America. An epidemic of CKD has led to the death of more than 20,000 lives in Central America. The disease primarily affects men working manually outdoors, and the major group affected is sugarcane workers. The disease presents with an asymptomatic rise in serum creatinine that progresses to end-stage renal disease over several years. Recent studies suggest that it is driven by recurrent dehydration in the hot climate. The epidemic is postulated to be increasing because of global warming. The epidemic of CKD in Mesoamerica may be due to chronic recurrent dehydration because of global warming and working conditions. This entity may be one of the first major diseases attributed to climate change and the greenhouse effect [79].

Glaser and more than 20 colleagues (2016) discussed climate change that has led to increases in the frequency and severity of heat waves (extreme heat events) and that one of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to acute mortality from exacerbations of pre-existing chronic disease and that inadequate hydration can lead to CKD that is distinct from that caused by diabetes, hypertension, or GN. Epidemics of CKD consistent with heat stress nephropathy are now occurring across the world [80].

**Debate:** ‘Should we consider renaming ‘Mesoamerican Nephropathy’ as Nephropathy of Unknown Cause in Agricultural Labourers (NUCAL)?’ [81].

Jayasumana et al (2016) suggest the name chronic interstitial nephritis in agricultural communities (CINAC). CINAC patients live and work in poor agricultural communities located in CINAC endemic areas with a hot tropical climate, and are exposed to toxic agrochemicals through work, by ingestion of contaminated food and water, or by inhalation. The disease is characterized by low or absent proteinuria, small kidneys with irregular contours in CKD stages 3-4 presenting tubulo-interstitial lesions and glomerulosclerosis at renal biopsy. Two different primary triggers have been proposed: one related to toxic exposures in the agricultural communities, the other related to heat stress with repeated episodes of dehydration heat stress and dehydration. Existing evidence supports occupational and environmental toxins as the primary trigger. The heat stress and dehydration hypothesis, however, cannot explain: why the incidence of CINAC went up along with increasing mechanization of paddy farming in the 1990s; the non-existence of CINAC in hotter northern Sri Lanka. This indicates that heat stress and dehydration may be a contributory or even a necessary risk factor, but which is not able to cause CINAC by itself [82].

Lozier et al (2016) propose a **case-definition** and a new name for CKDu; **chronic kidney disease of non-traditional cause CKDnT** [83]. CKDnT is suggested to be defined as a person age < 60 years with CKD, without type 1 diabetes mellitus, hypertensive diseases, and other well-known causes of CKD. A probable case of CKDnT is defined as a suspect case with the same findings confirmed three or more months later. CKDnT.

The concept of case-definition, which is very useful in surveillance programs, has been further developed [84]. In short, this proposal includes:

1) Estimated glomerular filtration rate (eGFR) <60 ml/ min/1.73 m².
2) and/or Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased eGFR: non-nephrotic proteinuria (albuminuria >30 and <3 000 mg/24 hours,) and/or urinary sediment abnormalities as markers of kidney damage (i.e., microscopic hematuria with abnormal erythrocytes morphology, or red blood cell casts, granular casts, or oval cells) and/or renal tubular disorders (i.e., renal tubular acidosis, nephrogenic diabetes insipidus, renal potassium wasting, other).

3) Age: 2 to 59 years.

4) Ultrasonography of the urinary tract demonstrating the presence of two morphologically symmetrical kidneys (eventually diminished in size), without urinary tract obstruction or renal polycystic disease.

Suggested exclusion criteria are:

1) Diabetes neuropathy) or history (current or previous) of nephrotic proteinuria.

2) Hypertension: BP (≥160/100).

3) Urologic pathology.

4) Primary glomerulopathy confirmed by renal biopsy or suspected due to presence of nephrotic-range proteinuria.

5) Hematologic disease.

6) Genetic and/or hereditary-familial renal disease.

7) Autoimmune.

8) Repeated exposure to X-ray contrast media and/or administration of phospho-soda solutions, as preparation for colonoscopy.

It is also recommended that in each case, record the following: 1) Residing or having resided for at least six months in an agricultural production area of Central America and 2) Working or having worked for at least six months in agricultural activities in Central America.

While appreciating the value and importance of this attempt, the suggested criteria become rather broad and will include many cases of undiagnosed kidney diseases of various types. At least if these criteria are used outside the high prevalence areas of MeN/CKDu/CKDnT. For example, many types of primary or secondary GN with non-nephrotic proteinuria that have not undergone diagnostic renal biopsy and different types of interstitial nephritis caused by infections and/or drugs, such as lithium. In fact – using these wide criteria a good number of CKDnT would be found in e.g. Sweden in northern Europe.

2017

Wijkstrom et al (2017 studied kidney biopsies from 19 male sugarcane workers in Nicaragua with suspected MeN in Nicaragua. Participants had a mean eGFR cr of 57 (range, 33-96) mL/min/1.73m2. 47% had low plasma sodium and 21% had low plasma potassium levels. 16 kidney biopsies were representative and showed glomerulosclerosis (mean, 38%), glomerular hypertrophy, and signs of chronic glomerular ischemia. Mild to moderate tubulointerstitial damage and mostly mild vascular changes were seen. The study confirms the renal morphology of MeN: chronic glomerular and tubulointerstitial damage with glomerulosclerosis and chronic glomerular ischemia. Follow-up urine and blood samples from both biopsy studies were collected to investigate the natural history.

In the follow up-study, median duration of follow-up was 13 (range, 13-27) months. Mean change in eGFRcr was -4.4 (range, -27.7 to 10.2) mL/min/1.73m2 per year [85].

In 2017 a group of clinicians and researchers described clinical and morphological findings in agricultural workers, mostly sugarcane, which may be the acute phase of Mesoamerican nephropathy (MeN) in Nicaragua. Over a 1-year period, physicians identified 247 mostly young (median 29
years), male (89.5%) patients with acutely elevated creatinine. This comprised 1.6% of the total workforce of about 15,000. Almost all patients presented to the hospital because of acute symptoms of illness such as nausea (59.4%), back pain (57.9%), fever (54.6%), vomiting (50.4%), headache (47.3%), and muscle weakness (45.0%) were common. Blood test revealed that leukocytosis (81%), and neutrophilia (86%) was common. Mean serum creatinine was 2.0 +/- 0.6 mg/dL. In urine almost, all patients displayed leukocyturia (98%), haematuria was also common (82%) and 34% had albuminuria exceeding 0.3 g/L. Bacteriuria was not seen. Patients were given supportive treatment with fluids intravenously but only 2% were prescribed antibiotics. Symptoms, clinical-, blood- and urine findings are well compatible with an acute inflammation and interstitial nephritis. In a follow-up CKD was later recorded in 8.5% of patients [86].

Largely the same group of investigators have also reported from examination of renal biopsies of 11 patients with suspected acute MeN in this Nicaraguan population [86], where the inclusion criteria was elevated serum creatinine, leucocyturia, and leucocytosis and/or neutrophilia. The renal biopsy showed tubulointerstitial nephritis, with varying degrees of inflammation and chronicity. Interstitial cellular infiltrates (predominantly T lymphocytes and monocytes), mostly in the corticomedullary junction; neutrophilic accumulation in the tubular lumens was prominent whereas the glomeruli were largely preserved albeit a few mild ischemic changes were observed. The acute components of tubulointerstitial nephritis were acute tubular cell injury, interstitial edema, and early fibrosis. Chronic tubulointerstitial nephritis included severe tubular atrophy, thickened tubular basement membrane, and interstitial fibrosis.

The morphological findings in this renal biopsy study differ from that of Wijkström et al 2015 and 2017 from MeN patients in El Salvador and Nicaragua respectively [24] [85] where interstitial inflammation was not prominent and glomerular changes observed. The case-mix is however very different; in the study of patients with acute MeN by [86] included leucocyturia, and leucocytosis and/or neutrophilia i.e. displaying acute evidence of ongoing acute inflammation and renal disease whereas Wijkstrom et al[24] [85] patients with established CKD taken, without signs of acute inflammation that were not currently working or exposed. Nevertheless the results by [86] that the chronic glomerular changes seen in typical cases of MeN may indeed by proceeded by acute interstitial inflammation. An observation that possible also have bearings on the proposed pathogenic process underlying chronic MeN. The acute interstitial inflammation suggests that dehydration and loss of electrolytes from heat stress is not the sole, perhaps not even the major cause, of acute MeN. However, heat stress may well contribute to the development of chronic CKD from MeN.

In an intervention study Wegman et al (2017) made an attempt to reduce kidney function damage from hard labour among sugarcane workers work in El Salvador by implementation a water, rest, shade (WRS) and efficiency intervention program. Cross-shift eGFR decrease was present in both groups; -10.5 mL/min/1.73m² [95% confidence interval (95% CI) -11.8 -9.1], but smaller for the intervention group after receiving the program. Decreased eGFR over the 5-month harvest was smaller in the intervention group -3.4 mL/min/1.73m² (95% CI -5.5 -1.3) than in the reference -5.3 (95% CI -7.9 -2.7) [87].

From Sri Lanka Gamage et al (2017) report a higher than expected rate of seropositivity to hanta virus in both CKDu patients and healthy in disease endemic compared to non-endemic areas of Sri Lanka. A subsequent report indicated that the residents in this area were in fact frequently infected with a virus similar to hanta; Thailand orthohantavirus or an antigenically related virus[88].

**Overview/review/discussion papers:** In a review paper al Orantes-Navarro (2017) points out that there has been an increase in what is considered as a form chronic interstitial nephritis in agricultural communities (CINAC) in certain countries which is not associated with traditional risk factors. This disease has become an important public health problem and is observed in several countries in Central America and Asia. The presence of toxicological, occupational, and environmental risk factors within these communities suggests a multifactorial aetiology for CINAC. This may include exposure to agrochemicals, a contaminated environment, repeated episodes of dehydration with heat stress, and an underlying genetic predisposition [89].
Madero et al. 2017 [90] in the journal *Current Opinion in Nephrology and Hypertension* gave a review on Mesoamerican nephropathy (MeN) and concluded that the evidence supports that recurrent cycles of heat stress, dehydration, and strenuous work may cause this type of CKD.

An epidemiologic review on the importance of pesticide exposures for the development of chronic kidney disease of unknown etiology was presented by Valcke et al. 2017 [91]. A systematic review was performed of the 21 analytical studies identified, seven were categorized as with low, ten with medium and four with relatively high explanation value. Thirteen (62%) studies reported one or more positive associations, but four had a low explanation value and three presented equivocal results. The main limitations of both positive and negative studies were unspecific and unquantified exposure measurement ('pesticides'), the cross-sectional nature of most studies, confounding and selection bias. No study investigated interactions between pesticides and other concomitant exposures in agricultural occupations, in particular heat stress and dehydration. It was concluded that existing studies provide scarce evidence for an association between pesticides and regional CKDu epidemics, but a role of nephrotoxic agrochemicals cannot be conclusively discarded.

In yet another review paper Johnson (2017) discussed that CKDu, or as is called in Central America, Mesoamerican Nephropathy, is now recognized in Central America, Mexico, India and Sri Lanka, and there is also some evidence that similar epidemics may be occurring in the USA, Thailand and elsewhere. A common denominator for each location is manually working outside in extremely hot environments. And that while some of the epidemics have been recognized by better reporting, the most important reasons are increasing heat extremes (heat waves) coupled with hydration with sugary or, less commonly, alcoholic beverages [92], while Zoccateli argued cyclic dehydration hypothesis alone could hardly explain the epidemics outside Mesoamerica [93] while Campese (2017) [94] suggested that the disease may be largely due to rehydration with large amounts of contaminated water.

A systematic literature search of epidemiological studies of CKDu in Central America has been reported by Gonzalez-Quiroz et al. (2017) [95]. Twenty-five epidemiological studies were included in the analysis of risk factors for CKDu. Increased prevalence odds ratio (POR) for CKDu were found males versus female gender 2.42 (95% CI 1.76–3.08), family history of CKD 1.84 (95% CI 1.37–2.30), high water intake (versus low) 1.61 (95% CI 1.01–2.21) and living at low altitude (versus highland) 2.09 (95% CI 1.00–3.17). However, there were no significant associations between CKDu and pesticide exposure (versus no) 1.17 (95% CI 0.87–1.46), alcohol consumption (versus no) 1.34 (95% CI 0.84–1.84), non-steroidal anti-inflammatory drugs (versus no) 0.99 (95% CI 0.60–1.39) and heat stress (versus no) 1.52 (95% CI 0.91 – 3.95).

Nerbass et al. (2017) [96] provide an in-depth review to examine the known effects of occupational heat stress on the kidney and concluded the extreme occupational heat stress combined with chronic dehydration may contribute to the development of CKD and ultimately kidney failure. Rising global temperatures, coupled with decreasing access to clean drinking water, may exacerbate the effects of heat exposure in both outdoor and indoor workers who are exposed to chronic heat stress and recurrent dehydration.

In the next issue of the same journal Herath et al. (2017 in press) [97] argue against the “heat stress/dehydration hypothesis” and also the proposal that global warming over the last half-century has been sufficient to have caused a drastic change in renal function in manual workers in hot climates.

Kidney Diseases in Agricultural

2018

Wijkstrom et al. 2018 [98] conducted a renal biopsy study in Sri Lanka to compare clinical and morphological findings in patients with CKDu in this country with the MeN morphology from Central America. Eleven patients with CKDu using similar inclusion and exclusion criteria as previous MeN studies were recruited. Participants were between 27-61 years of age and had a mean eGFR of 38+/−14 ml/min/1.73m2. Main findings in the biopsies were chronic glomerular and tubulointerstitial damage with glomerulosclerosis (8-75%), glomerular hypertrophy and mild to moderate tubulointerstitial
changes. The morphology was more heterogeneous and interstitial inflammation and vascular changes were more common compared to previous studies of MeN. In two patients the biopsies showed morphological signs of acute pyelonephritis, but urine cultures were negative. Electrolyte disturbances with low levels of serum sodium, potassium, and/or magnesium were common. In the urine, only four patients displayed albuminuria, but many patients exhibited elevated alpha-1-microglobulin and magnesium levels. There are many similarities in the biochemical and morphological profile of the CKDu endemics in Central America and Sri Lanka, but there were differences, such as a more mixed morphology, more interstitial inflammation and vascular changes in Sri Lankan patients.

From Nicaragua [99] in 2018 report on the risk of acute injury in sugarcane workers. 326 sugarcane workers with normal serum creatinine and no history of CKD working in a high prevalence area of CKD/MeN in Nicaragua were examined at the end of the harvest season. 34(10%) of 326 tested displayed a Scr level increase ≥ 1.3 mg/dL (corresponds to a p-creatinine of < 115 umol/l). Elevated Scr (called Acute Kidney Injury (AKI) in the report) was more common among cane cutters. Follow-up of 29 and 24 of those with elevated Scr after 6 and 12 months showed that average Scr went down (increased eGFR) from 1.64 mg/dl to 1.25 and 1.27. However, 7(24%) of the 29 before harvest healthy men that was tested at least once displayed evidence eGFR < 60 ml/min 6-12 months after the harvest season. Taken at their face these data suggest that roughly 2-3% of employed healthy men may develop CKD after a harvest season.

From Guatemala (2018) at has been reported that sugarcane cutters with lowered renal function, eGFR< 60 ml/min, 2% of a total workforce of 4095 tested, had lower productivity than those with eGFR > 60 ml/min and this was in particular seen at high, WBGT from 30 up to 34C [100]. A large proportion of the hired men left work during the half-year of cane harvesting, and those with impaired renal function were prone to this; 42 versus 25% of men hired.

In a similar follow-up study of the kidney function over the 6-month harvest period of 330 sugarcane cutters was done in Guatemala [101]. Albeit a decline in kidney function across the harvest was observed in 36% of the participants the average eGFR for the whole group did not change and only 3% had eGFR <60 ml/min. The drop in eGFR noted for one third of the examined group may well an effect of random variation as similar sized group displayed increased eGFR. This is however not the conclusion of the authors who conclude that both occupational and behavioural factors play significant roles in declines in kidney function.

In another report from Guatemala Cross-shift changes in kidney function of sugarcane workers was examined [102]. 105 healthy sugarcane workers were followed. Pre-harvest clinical data as well as daily environmental, clinical, and productivity data for each worker was assessed. Post-shift p-creatinine levels were significantly higher than pre-shift values (eGFR dropped on average 25%) but there was no evidence of eGFR (pre- or post-shift) to decrease over the three months observation period. The short term (post-shift) increase in p-creatinine, according to my interpretation, more likely to indicate changes in the muscle- and protein metabolism, than actual effect in the GFR. It can theoretically be shown that also a rather dramatic decrease in the GFR will not be evident in plasma until at least 8 hours has passed A 50% drop in GFR increase p-creatinine with only produce an increase in p-creatinine of about 20 umol/l after 8 h. Principles, and rather sophisticated theoretical ad mathematical background, for interpreting p-creatinine when GFR is rapidly changing has been presented [103].

Gonzalez-Quiroz and collaborators have reported remarkable results from a 2-year community-based prospective cohort study of kidney function in a young rural population 520 young adults (286 males and 234 females) in the 9 different communities of Northwest Nicaragua severely affected by CKD [104]. After exclusion of individuals with known, or self-reported, kidney disease 350 agreed to participate. The natural history of, and factors associated with, loss of kidney function was examined every 6 months a 2-year period. eGFR was assessed by p-creatinine and cystatin C. Among men 81% remained stable, 9.5% experienced rapid decline in eGFR of -18.2 ml/min per 1.73 m(2) per year), and 9.5% that had a baseline dysfunction (58 ml/min per 1.73 m(2) experienced an average drop in eGFR of -3.8 ml/min per 1.73 m(2) per year. Among women: 96.6% remained stable and 3.4% experienced rapid decline. Among men, outdoor and agricultural work and lack of shade availability during work
breaks, reported at baseline, were associated with rapid decline. Urinary NGAL concentrations were higher in men with low kidney function at baseline and among those that experienced rapid drop in eGFR[105].

In a logistic model to predict prediction rapid eGFR decline however U-NAGL alone was not able to predict individuals with rapidly declining eGFR[106].

Another important follow-up study of the kidney function was published from an area in the Pacific low-land of Nicaragua with an established high prevalence of CKD/Men in 2018 [107]. From February 2015 to May 2017, 586 previously overall healthy agricultural workers (median age 27.8 years, 90% male) presented with symptoms and signs of acute Men was followed. The majority had a normal baseline creatinine, but leukocyturia (98.8%) and peripheral leukocytosis (80.7%) were common. Within 6 months 8.4% individuals with acute Men progressed to some level of CKD and 5.5% to eGFR < 60 ml/min. The strongest predictors of CKD progression were anemia and paresthesias at presentation, while leukocytosis was associated with renal recovery. High blood uric acid, low p-sodium (< 135 mmol/l) and low p-magnesium was much more common among those that progressed to CKD.

A group of researchers from Pan American Health organisation (PAHO) [108] present Chronic kidney disease mortality trends in selected Central America countries, 1997-2013 and clues to cause of the CKD epidemic, now renamed from CKDnT to of chronic interstitial nephritis of agricultural communities (CINAC).

It is shown (see figure) that the age adjusted mortality rate in chronic kidney disease (ICD CKD-N18) among males is markedly higher in El Salvador and Nicaragua as compared to USA, Panama, Costa Rica and Cuba, and furthermore that the rates are rapidly increasing. Based on temporal associations and increasing rates of CKD mortality in parallel to the rapidly and unsafe use of agrochemicals that has been reported from Central America [109]. One major problem in the interpretation of these data on mortality in CKD in different countries is the uptake in renal replacement therapy (RRT) of patients with end stage renal disease (ESRD) in the different countries. If a CKD patient enters RRT they rarely die from CKD but from complications of ESRD such as CVD and infections in will then not be recorded as death from CKD. The uptake rate in RRT the countries in the figure varies much, depending on resources available for health care and RRT. In the US the uptake in RRT at age 45-64 is close to 60 per 100,000 inhabitants. There are also substantial differences in incidence of starting RRT between different socioeconomic groups. The incidence of RRT is much higher for non-whites and native Americans. Thus, the striking differences in CVD displayed in the figure most likely is influenced by differences in uptake rate in RRT.

Overview/review/discussion papers: A literature review on Sugarcane cutting work, risks, and health effects was provided in 2018 [110]. The inclusion criteria were articles published between January 1997 and June 2017, which evaluated working conditions and health effects on sugarcane cutters. From the 89 articles found, 52 met the selection criteria and were evaluated. It was concluded that manual cutting of sugarcane, especially of burned sugarcane, exposes workers to various risks, with
different health impacts. Risk reduction for exposure to pollution and thermal and physical overload is required as a measure to preserve the health of the worker.

Pedro Ordunez in the scientific journal Kidney International [111] summarizes a 54-page document from the Pan American Health organisation (PAHO) on diagnosing and surveillance of CKDnT [111]. This PAHO document presents a background to the CKD epidemic, including its epidemiology and updated mortality estimates. The paper present case definitions of CKDnT developed for the purposes of CKDnT surveillance. A multideterminant model of causation is suggested [111].

Ordunez and associated researchers has in several review and overview papers suggested that exposure to agrochemicals and pesticides have an important role in the CKD, if not the sole cause most likely contributing to the epidemic [112] [108]. However, this association between CKD and agrochemicals/pesticides is mainly circumstantial and there are limited epidemiological or toxicological evidence to support this. Elinder at al [59]in a review wrote ‘Although pesticides can be responsible for both acute and occasionally chronic health effects [113], they are rarely nephrotoxic unless associated with a serious systemic intoxication with multiorgan damage [114]. A parallel might be made; If a crook happens to pass the scene of a crime he is not necessary the culprit!’

Marc E. De Broe and associates [97] in this review paper argue fiercely against Heat-Stress Nephropathy. The authors appreciate the emergence of a new chronic tubulo-interstitial kidney disease of uncertain cause among agricultural communities in Central America and Sri Lanka, but claims that there is sparse evidence for the occurrence of significant AKI among manual workers who are at high risk, and that there is little substantial evidence that an elevation of serum creatinine < 0.3 mg/dl in previously healthy people will lead to CKD even with recurrent episodes. It is also stated that the mechanisms of heat stress causing CKD have not yet been proved in humans or demonstrated in workers at risk. It is believed that claims of a global warming nephropathy in relation to this disease may be premature and without convincing evidence.

2019

A high a prevalence of CKD has also reported from Uddanam in Western India [115]. 2210 individuals (age >18 years) living in a rural area were examined. CKD with eGFR <60 ml/min per 1.73 m² was seen in 14%. Of these less than 20% had proteinuria. Major risk factors, such as diabetes, long-standing hypertension, and significant proteinuria, were absent in most (73%) of patients with CKD, which is then compatible with CKDnU. It was concluded that CKDu is a ‘true public health threat in Uddanam’.

In another Indian report prevalence of lowered eGFR in different Indian populations; Urban and rural areas of Northern India (states of Delhi and Haryana) and Southern India (states of Tamil Nadu and Andhra Pradesh) was compared [116]. 12 500 individuals without diabetes, hypertension or heavy proteinuria was examined between 2010 and 2014. The prevalence overall prevalence of eGFR <60 ml/min per 1.73 m² was 1.6%, but this figure varied markedly between areas, being highest in rural areas of Southern Indian (4.8%). In Southern India, risk factors for eGFR <60, were residence in a rural area, older age and less education. Among individuals aged less than 49 the prevalence ratio of eGFR below 60 ml/min per 1.73 m² was 5 to 6 times a for rural versus urban residents. It is suggested that the CKDu epidemic is not confined to Central America and Sri Lanka.

**Overview/review/discussion papers:** Yet another non-critical review suggesting a role of heavy metals such as cadmium and lead for the endemic of CKDu in Sri Lanka has been published but provides no new or pertinent information [117].

In early 2019 researchers at the Pan American Health Organization (PAHO) presented a systematic review of the most frequent exposures suspected to be possible causes of CKDnT[118]. Four systematic reviews and 61 primary studies from many different countries, among these China, Taiwan and Tanzania i.e. outside the typically CKD endemic areas, were included. Results of the meta-
analysis reached significance for working in agriculture, and when cross-sectional studies were excluded, agrochemical exposure also became significant. Why cross-sectional studies this should be excluded was not explained. Exposure to heat-stress, not very precisely defined, was not significantly associate with an increased risk. Albeit this review is systematic it seems to use of very crude assessments of possible pertinent exposures and appear to be too much of ‘mixing apples and oranges’ to allow any conclusions on likely and less likely causes/contributors of CKDnT.
Additional papers and facts that may be pertinent in the context of discussions of CKDu and MeN that may relevant to cite and consider;

Second International conference on Mesoamerican Nephropathy 2015 [119].

Thesis of Julia Wijkström, which present clinical and renal morphology data from patients with CKDu from three counties, El Salvador, Nicaragua and Sri Lanka [120]

Jah and Modi in a review paper for Kidney International [121]. The estimated global crude prevalence of CKD is was about 150 per million in 1990, which increased to 275 per million cases in 2016. This change in prevalence is mostly related to ageing. It is pointed out that the adverse health impact from CKD is not limited to end-stage kidney failure.

In 2014 a previously ill-defined autosomal dominant renal diseases which originate from tubular cells and lead to tubular atrophy and interstitial fibrosis was described in more detail [122]. Ten families were examined, and specific mutations was found in 7 of 9 families. On the basis of clinical and pathological characteristics we propose the term ‘Autosomal Dominant Tubulointerstitial Kidney Disease’ was suggested. The morphological changes described to are not identical but share similarities with those seen in MeN.

Kew at el already in 1970 reported that acute renal damage was a common and important complication of heatstroke among South African goldminers, but that this sometimes may progress to CKD. The effects of heatstroke on renal structure and function have been studied in 40 Bantu gold-miners. During the acute stage all showed evidence of renal damage, which was classified as mild in 19, moderate in 12, e 10 of those with moderate damage have were followed for periods of up to four years with serial studies of renal function and structure. In the majority of both severe and moderate cases the impaired renal function of the acute stage was completely reversible, and renal histology either returned to normal or showed only a minimal degree of residual patchy interstitial fibrosis. However, four of the patients subsequently developed chronic progressive interstitial nephritis with persistent or progressive impairment of renal function [123].

D’Haese et al. (2008) [124]. In the chapter Organic solvents, silicon-containing compounds and pesticide, Clinical Nephrotoxins. Renal Injury from Drugs and Chemicals by M. E. De Broe and G. A. Porter, present that AKI from pesticides is mainly seen in connection with full-blown systemic toxicity from pesticides.

A special issue in the Lancet [125] was in 2018 devoted to health consequences of climate change. In this report focus is given to decreased outdoor labour productivity and migration and socio-economic consequences. Soma attention is given to the possibility of an increase of infectious diseases, such as dengue fever. Kidney diseases and CKD is not discussed.
Some aspects on using p-creatinine and/or cystatin to estimate the glomerular filtration rate (GFR).

Measurement of plasma or serum) makes it possible estimate the glomerular function (eGFR) with reasonably accuracy. Age and gender has to be considered and a sophisticated formula used; usually the so called CKD-epi formula. In the US also ethnicity; black or non-black, is needed. Measurement of a cystatin C, a small plasma protein, can also be used for eGFR with similar good accuracy. A thorough systematic review on which estimate of eGFR that provided the best accuracy under different conditions (age, gender and various GFR ranges) from Sweden [126, 127] concluded that creatinine and cystatin C provide equally and reasonably accurate eGFR, and that the average of these to eGFR (creatinine) and eGFR (cystatin C) is even more accurate.

eGFR from cystatin C has some important advantages though, it’s not influenced by muscle mass or ingestion of meat and creatinine rich food such as meat goulash. A few hours after a goulash serving containing 250-300 of meat the p-creatinine concentration double [128]. An increase in p-creatinine of about 20 umol/l is typically seen 3-4 h after meat containing meals as compared to non-meat meals, whereas cystatin C remains unchanged [129]. Heavy physical exercise may also change the p-creatinine concentration. After a marathon run, or worse, p-creatinine on average may increase with 10-30 umol/l [130] whereas the increase in cystatin C is much less pronounced [131].

Another, and often neglected factor when interpreting p-creatinine changes and eGFR, is that the calculations behind eGFR presume a stable renal function (GFR). A sudden drop in GFR will not result in increasing p-creatinine until sometime has passed. This because of basic pharmacokinetic principles. When assessing and treating acute kidney injury specific formulas, based on the change of p-creatinine over time, has been suggested to calculate the actual change in GFR [103]. From pharmacokinetics of creatinine, which is produced at a more or less constant rate from the muscle cells, I’ve calculated that a sudden 50% drop in the GFR will produce merely a 20% increase in creatinine after 8h. This latency of achieving a new steady-state level of creatinine in plasma (enabling accurate eGFR calculations) possibly hold true also for p-cystatin C.
Prevalence of CKD in relation to age in ‘normal’ population.

This figure, which present the proportion on different eGFR levels in different age groups in Sweden [132], may serve as a reference to compare results from cross-sectional studies cited above.
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