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Mesoamerican Nephropathy (MeN): A 'New' Chronic Kidney Disease related to Occupational Heat Exposure with Repeated Deprivation of Salts and Water

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Introduction

In the early 2000 awareness among people and health workers in the Mesoamerica's slowly emerged that a chronic kidney disease (CKD) was prevalent among poor male sugarcane workers. Initially it was considered as chronic kidney disease of unknown cause (CKDu) [1], later it was called 'Sugar Cane Nephropathy' as mostly sugar cane workers were affected. At the International Society of Nephrology meeting in Vancouver 2011 Ricardo Correa-Rotter coined the name Mesoamerican Endemic Nephropathy (MEN) in view of the fact that it was seen also among cotton workers and the history of another geographically endemic kidney disease which for many years had an enigmatic cause; Balkan endemic nephropathy [2,3].

At the first international scientific meeting in Costa Rica in late 2012 on this 'new' kidney disease it was recognized that a very similar type of chronic disease probably occurred among agricultural workers in other hot countries, in particular Sri Lanka, and it was decided to omit the word 'endemic' and to call this disease Mesoamerican Nephropathy (MeN) based on the area where this new type of CKD was first characterized [4-6].

MeN typically are characterized by an insidious development of CKD with a lowering of the estimated glomerular filtration rate (eGFR) without common risk factors as hypertension, diabetes, obesity or macroalbuminuria [6]. End stage renal disease can develop and if renal replacement therapy (RRT) is not available the patient may eventually die from uraemia. It was are markably high proportion of CKD from unknown cause among recently started dialysis patients [7] and high mortality from CKD in certain areas of *El Salvador* and Nicaragua that first draw attention to the epidemic [8]. By referring to national statistics in Nicaragua and *El Salvador* it has been concluded that the epidemic of MeN (or CKDu) in Central America 'results in many thousands of deaths' [1,9]. As mainly relatively young men working in plantations are affected it was early suggested that some sort of occupational exposure was involved in the pathogeneses, in particular exposure to pesticides [10]. However later research have concluded the epidemic is possibly caused by repeated episodes of heat stress with concomitant dehydration and loss of essential minerals during heavy work in hot climates. Possible co-factors include excess use of nonsteroidal anti-inflammatory drugs (NSAIDs) and fructose consumption in rehydration fluids [5].

There are also reports on a high incidence of CKDu from certain areas of Sri Lanka [11,12]. As in Central America mainly poor agricultural workers are affected. Also in Sri Lanka exposure to agrochemicals where initially suspected, but more recently also dehydration considered to be of major importance [13].

Lately data from renal biopsies and detailed clinical description on individuals with MeN have been presented [14-16] showing specific histopathological changes in renal biopsies from persons with MeN, findings which are also in concert with the hypothesis that repeated heat stress, dehydration and loss of sodium and potassium is a major causative pathway.

Epidemiology

Morbidity and mortality

The first publications on the CKDu epidemic in Central America possibly came 2002 [7], a hospital study of 205 new dialysis patients 1999–2000 in *El Salvador*. For 135 of these, the cause of kidney failure was unknown. These patients were predominantly men (87%) had average age of 51 where 63% had worked in agriculture and 73% had been exposed to agrochemicals. The authors suggested exposure to toxic chemicals as a possible causal factor.

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 in the Pacific lowlands [8]. The age standardized mortality rate due to chronic kidney diseases (coded as N18 (CKD-N18) by the 2010 International Classification of Diseases) is notably higher 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 [17]. The geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica have been examined. 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 [18].

Hospital admissions rates of unspecified CKD and non-diabetic ESRD, 16,384 and 8,342 respectively in 242 municipalities have been analysed in *El Salvador* 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°C) in *El Salvador*. Percent area of sugarcane cultivation produced the greatest bivariate regressions. However, when models where made more complex multivariate and sophisticated, the association with heat became less evident [19]. The enrolment rates of RRT in Guatemala have been analysed and found to be significantly higher 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 [20].

Cross-sectional and clinical surveys

From *El Salvador:* In 2005 [10] 291 men living in the Pacific coast line of *El Salvador* was examined and a high prevalence of CKD (13%) was found. Men diagnosed with CKD had 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 two thirds did not have a known cause for CKD and did not have proteinuria. Being a farmer, pesticides exposure and alcohol consumption were found to be very common characteristics in both populations. In another region of *El Salvador,* Bajo Lempa, eGFR was calculated from serum creatinine using the MDRD formula in 775 persons (343 men) [21]. The prevalence of eGFR<60 ml/min per 1.73 m^2 was 17% in men and 4% in women. Aetiology was not diabetes, obesity, or hypertension but considered to be 'unknown' in most of the cases. However there were clear associations with agricultural work.

A more extensive cross-sectional study in five populations of *El Salvador* in five communities, rural coastal sugarcane, semirural coastal sugarcane, high-altitude sugarcane, coffee and urban was reported 2012 [22]. Altogether 664 persons were examined with measurements of blood pressure, serum creatinine and urinary paper test strips. Occupational exposure and some basic information of life style and medical history were also obtained. 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 m^2 among men was 19% and 18%, whereas the prevalence of low eGFR in the high-altitude sugarcane, coffee and urban population was less than2%. In a multivariate logistic regression analysis work on sugarcane or cotton plantation came out as the strongest predictor; 3.1 (CI 2.0-5.0) among men for each 10 year period. The increase in 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 m^2 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.

A population screening study in *El Salvador* was reported in 2014 [23] 2,388 individuals in three agricultural communities were examined; Bajo Lempa, Guayapa Abajo and Las Brisas (976 men). The prevalence of CKD (eGFR<60 mL/min/1.73 m^2) was high in all three villages, 6.8% in women and 17% in men and increased with age. At age >60, CKD was present in 57% of the men and in 28% of the women. 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 male agricultural works compared to non-agricultural workers. Contact with of agrochemicals was common among men and reported by 54% of the men and 15% of women. Use of NSAIDs was overall common and similar in both sexes (84% in men and women). The authors 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' probably are involved. The same year yet another descriptive cross-sectional study from two Salvadoran farming communities; Dimas Rodríguez (El Paisnal municipality) and El Jícaro (San Agustín municipality) facing the Pacific reported a high prevalence of CKD: A total of 223 persons were studied. Overall prevalence of chronic kidney disease (CKD 3 or higher) was 11% men and 21% in women. It is noteworthy that CKD was more common in women than in men in this study. Most of the examined reported farming occupation and contacts with agrochemicals [24]. In a cross-sectional study 2009 - 2011, 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) were screened. eGFR was calculated from the CKD-EPI formula. Prevalence of CKD (eGFR<60 ml/min/1.73 m^2) was 13.9%. 5.7% had microalbuminuria (30-300 mg/L) and 0.8% macroalbuminuria (>300 mg/L). Information of various risk factors was 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 [25].

From *Nicaragua:* In a health examination 1,096 persons living in five different villages in the north western part of the country participated and provided blood and urine for analysis. 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. Likewise the prevalence of eGFR<60 ml/min per 1.73 m^2 calculated using the MDRD formula. Proteinuria, measured by paper strip was recorded in about one third of those with eGFR<60 ml/min per 1.73 m^2. It was noted the high CKD prevalent villages were located at a low altitude close to the pacific coast and it was suggested that heavy workload in a hot climate leading to repeated dehydration may be one explanation [26].

In another report from north western *Nicaragua* [27] blood samples were obtained from 997 individuals and eGFR calculated (using the MDRD formula) from analysis of plasma creatinine. 12.4% were identified as having an eGFR<60 ml/min per 1.73 m^2. In a case- control approach various exposure and demographic factors where compared with those having an eGFR>60 ml/min per 1.73 m^2. In a multivariable analysis age, male genders, low BMI, agricultural work, several other types of occupations but not exposure to pesticides were related to a low eGFR. Reported consumption of 'lija' which a type of locally brewed liquor, and large amounts of 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.

A third large cross-sectional study, in Quezalguaque a municipality in County of Leon at the pacific coast in *Nicaragua*, was published 2011, 771 participated. The prevalence of lowered eGFR (eGFR<60 ml/min per 1.73 m^2, CKD stage 3 and 4) was overall high (8.7%), 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, derived 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 m^2) 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. Hypertension or diabetes mellitus was not associated with CKD in the study [28].

It is important to recognize that all areas of *Nicaragua* are not affected by the CKD epidemic. In a cross-sectional study on the renal function in 267 (147 women) residents aged 20-60 years living in a village in the north-central part of *Nicaragua*, where coffee cultivation is the main source of employment, were studied and there was no evidence of a high prevalence of CKD [29]. Being situated 1000 meters above sea level the village has a colder climate in comparison with villages along the Pacific coast line. 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 1.73 m^2. Macroalbuminuria, as assessed by urine dip stick, 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 provides support for the notion that heat exposure rather than pesticides are involved in the causative pathway of MeN.

In 2014 a report came from one of the most affected communities, located near the town of Chichigalpa in *Nicaragua* [30]. 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 dip stick 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 m^2 was found to be as high as 42% in the male and 9.8% in the female population. Among participants with eGFR <60 mL/min/1.73 m^2, 44% had mild proteinuria ≥ 30 mg/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 eGFR calculation <60 mL/min/1.73 m^2 and controls defined by an eGFR >90 mL/min/1.73 m^2. 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. NSAID use was common, >70% in both cases and controls and there was no significant difference between cases and controls. Aside from age and male sex, cutting sugarcane during dry season was found to have the strongest independent association with reduced kidney function. 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 [30]. Reported chewing sugarcane was significant (OR 2.7, 95% CI 1.1–6.8).

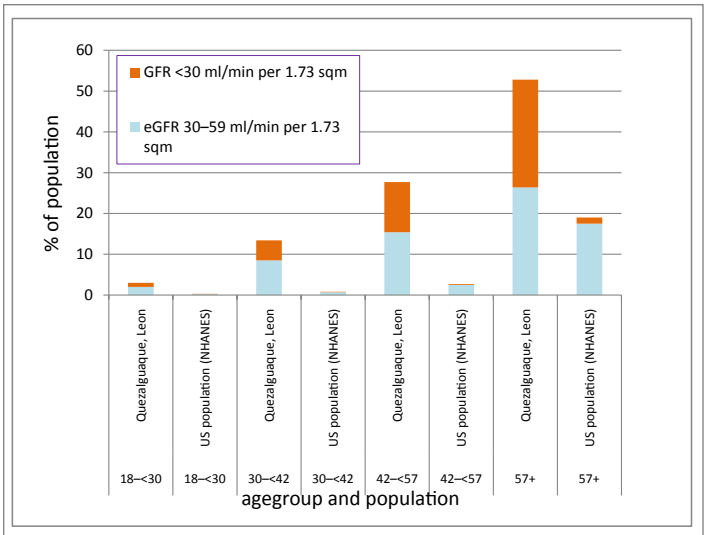

Figure 1: Figure 1 derived from O'Donnell et al.[28], present the prevalence of lowered eGFR (eGFR 30-59 ml/min per 1.73 m^2 or <30 ml/min per 1.73 m^2 in different age-groups of examined men in Leon, Nicaragua compared to NHANES figures from the US male population.

In another recently published cross-sectional study from Leon, 2,275 individuals were included. CKD (eGFR<60 ml/min/1.73 m^2) prevalence was 9.1%; twice as high for males (13.8%) than females (5.8%). Reduced kidney function was significantly and dose-response associated with age, rural areas, low education level, and self-reported hypertension, high daily liquid intake, lija (moonshine) consumption and years of agricultural work.. This study provides additional support for an environmental and/or occupational cause of MeN [31].

From *Sri Lanka:* Chronic kidney disease (CKD) is also an emerging as a major health problem in *Sri Lanka*. In order to examine risk factors 183 patients with CKD of unknown aetiology were recruited randomly from among patients at Anuradhapura Hospital (n=136 males and n=47 females) [11]. These were patients with a serum creatinine concentration greater than 2 mg/dl but with no obvious underlying cause. A control group of 200 subjects (n= 39 males and n=61 females) in the age group 36 to 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 Ayurveda treatment (Hindu traditional medicine) in the past and a past history of snake bite were more common among patients with CKD compared with controls. Although initial analysis indicated that being a farmer and use of pesticides were associated with CKD, in the multivariate model, exposure to pesticides did not impact on the development of CKD. More specific information on individuals with CKD in Sri Lanka has been provided later [12]. Screening for proteinuria was done in three areas; Medawachchiya, Yatinuwara 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 m^2. The proteinuria in most of the cases was relatively low and few had hypertension. 26 of 109 patients from Medawachchiya with proteinuria underwent a renal biopsy. The light microscopic findings were indicative of tubulo-interstitial disease, whereas the immunofluorescence tests for immune-mediated kidney injury 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 to dehydration and environmental toxins than other populations of Sri Lanka.

Etiology

Repeated dehydration, loss of sodium and potassium, and heat strain hypothesis

At the first international MeN meeting there was a general consensus that repeated episodes with dehydration during heavy work in hot climates with loss of electrolytes and minerals with attending AKI is the leading pathway to cause the epidemic of CKDu in Central America [4]. It was emphasized that the most affected group in Mesoamerica are sugarcane cutters, exposed to extreme ambient heat during hard physical work [32]. 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 [5]. 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 [33]. Correa-Rotter et al. [6] provide a more in depth presentation from the first international MeN meeting 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, 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 cause 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.

The latter theory was supported by morphological examinations of renal biopsies from MeN affected individuals showing glomerular changes indicative of glomerular ischemia despite only minor vascular changes. Possible explanation for this finding could be chronic ischemia due to dehydration and, in many cases, a combination with frequent intake of NSAIDs which per se could affect renal hemodynamics. However all patients with MeN have not used NSAID. Furthermore it has been 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 pathogenesis [14].

That sugar cane harvesting may indeed bring about signs of acute kidney injury has been shown in field studies from Brazil [34]. Twenty-eight healthy non-African Brazilian workers engaged in sugar cane harvesting during 2009 were examined. Blood and urine samples were collected before the harvest season, and before and after a 9 hour workday during harvest season. Although there were no difference in p-creatinine at start of the harvesting season and a morning sample at the end of the harvest season, p-creatinine at the end the workday had increased in all men (average 0.21 μmol/l), and eGFR dropped on average about 20 ml/min per 1.73 m^2 and five men (18%) displayed acute kidney injury diagnosed by the p-creatinine increase. During the harvesting season the men worked from 0700 to 1600 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 [34].

In recent years it has also become increasingly evident that repeated episodes of acute kidney injury (AKI) may precipitate and develop into CKD [35,36].

That heat exposure during sugarcane harvesting is considerable has been shown in Costa Rica. Non-participatory observation and Wet Bulb Globe Temperatures (WBGT) measurements were carried out during two typical working weeks in 2012 and 2011 in Guanacaste, in north western Costa Rica. Sugarcane in this area is typically burnt the night before harvesting. Already at 7:30, after only one or two hours of work, the OSHA (Occupational Health & Safety Administration, USA) limited of 26.0°C WBGT was attained on most days. At 9.15 am the WBGT was often 30.0°C and at this level OSHA guidelines are to only work 15 minutes per hour to avoid health risks. Nevertheless, the sugarcane workers typically continued working for several more hours to get a better income, which is based on the weight of the cut [32].

Another way to elucidate the cause of MeN was done by a team from Boston University School of Public Health [37]. Semi-structured interviews were performed with 10 physicians and 9 pharmacists in North-western Nicaragua i.e. in areas with a high prevalence of chronic kidney disease (CKD) of unknown cause. The physicians and pharmacists regarded CKD as a major problem in the region, predominantly affecting men working with manual labour. The interviewed health professionals believed occupational and environmental sun and heat exposure as well as dehydration to be risk factors in the development of CKD. These risk factors were also thought to be associated with a set of symptoms referred to locally as "chistata," characterized by painful urination and often accompanied by "kidney" and/or back pain. The interviewees indicated that reluctance among workers to drink water during the work day might be due to perceptions of water contamination. "Chiasta" symptoms were often treated with non-steroidal anti-inflammatory drugs, diuretics or antibiotics. Albeit the diagnosis of urinary tract infection was sometimes set ant treated with antibiotics this diagnose was usually not based on microbial culture. The incidence renal stones were not considered to 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 [37].

Changes and job-specific differences in the renal function over a 6-month sugarcane harvest season in 284 Nicaraguan sugarcane workers performing seven distinct tasks as; cane cutters, seeders, seed cutters, agrochemical applicators, irrigators, drivers and factory workers has been investigated [38]. In all groups considered to be exposed to "heat stress" eGFR (CKD-EPI equation) decreased during harvest and significantly decreased in seed cutters (-4.5 ml/min/1.73 m^2) and irrigators (-4.9 ml/min/1.73 m^2) but was not seen in the groups without "heat stress" (drivers and factory workers). 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. 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 [39]. Thus the examined group to some extent comprise a selection of healthy individuals.

Further support dehydration and loss of minerals being the major cause of MeN have recently been presented from *El Salvador* [40]. 189 sugarcane cutters aged 18–49 years; mostly males in *El Salvador* were examined before and after a work day. They found that serum uric acid

levels measured before the shift were unusually high. eGFR levels before the shift were (<60 mL/min 1.73 m² in 23 male participants. The mean work-time was 4 hours and the mean temperature was 34–42°C. The mean consumption of liquids during the work day was 0.8 L per hour. Urine osmolality and urine creatinine increased while urinary pH decreased. There was also an increase in serum creatinine and uric acid while potassium and chloride decreased. The authors conclude that the changes are consistent with repetitive volume depletion caused by heavy manual labour in a hot climate. They also speculate that a pathophysiology could include reduced blood flow in the.

Based on animal experiments, fructokinase activity and fructose metabolism may be promoting a dehydration-induced acute kidney injury to CKD [41]. This has been elucidated in an animal model [42]. Wild-type mice and fructokinase-knockout mice were subjected to repetitive 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 developed signs of renal damage, as noted by an increase in serum creatinine, urinary neutrophil gelatinase-associated lipocalin (NGAL) and renal MCP-1. In biopsies proximal tubular injury with macrophage infiltration and early renal fibrosis was found. The authors suggest an activation of the polyol pathway, because of increased levels of sorbitol and fructose in the renal cortex. Mice that were exposed to the same heat but who hydrated during the day were mostly 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 [42].

Alternative hypothesis

The arsenic concentration in urine from CKDu patients (n=125) and controls without CKD (n=180) was analysed by researchers in Sri Lanka [43]. Urine arsenic levels were found to be above 21µg/g creatinine in 68% of the CKDu cases and 28% of the control cases. . It was suggested that arsenic exposure from contaminated agrochemical formulations might be involved in the pathogenesis of CKDu. However, albeit inorganic arsenic is severely toxic and may cause several types of systemic toxicity, kidney toxicity, in particular in the form of lowered eGFR, has rarely been reported [44]. Furthermore monitoring of exposure to the toxic form of arsenic (i.e. inorganic arsenic) is complicated by the fact that an organic form 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.

Contact with various different types of pesticides and agrochemicals are common in MeN endemic areas. Contact and inhalation with pesticides has been proposed as a risk factor [30]. However, not all reports have supported the association between pesticides and CKD. In Nicaragua a case-control study including 997 people (12.4% had CKD) did not find an association between low eGFR and exposure to pesticides [27].

Although pesticides can be responsible for both acute and occasionally chronic health effects [45], they are rarely nephrotoxic unless associated with a serious systemic intoxication with multiorgan damage [46]. A parallel might be made; If a crook happens to pass the scene of a crime he is not necessary the culprit!

However, a report suggesting an association between pesticides and end stage renal disease have recently been published [47]. The association between exposure to 39 specific pesticides and end-stage renal disease (ESRD) incidence in a cohort study of licensed pesticide applicators was evaluated in the US. 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 [47]. In view of the large number of statistical analysis that was made this study and the rather non-specific outcome (ESRD), risk for confounding from other factors this study do not strongly indicate that MeN is caused by exposure to pesticides.

At has also been suggested that the culprit of the ongoing epidemic of CKD in rice paddy farming areas of Sri Lanka is the commonly 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. However the evidence presented is as yet, mainly circumstantial [48].

In a review and update of what is known about CKDu that has emerged in the north-central dry zone of Sri Lanka 16 manuscripts and three abstracts were included [49]. The CKDu prevalence was 5.1%–16.9% and more common in men. Most patients with mild to moderate CKD were asymptomatic; urine protein <1 g/24 hours and kidneys were small on ultrasound. The main finding in renal biopsies was interstitial fibrosis. Heterogeneity of definitions and methodologies in the studies examined limit the possibility of conclusions regarding possible cause(s). The author suggests that aetiology of CKDu in north-central Sri Lanka is multifactorial, involving one or more environmental agents and possibly genetic predisposition in vulnerable populations [49].

Different inclusion- and exclusion criteria and lack of distinctive criteria for CKDu diagnosis was a problem in interpreting the various study results. Almost all studies seem to be based on screening for proteinuria rather than a low eGFR. This makes comparisons with the cross-sectional studies is Central America difficult as many of the individuals in the Central American studies with lowered eGFR do not display proteinuria. However, as in Central America, in Sri Lanka no association was found with conventional risk factors for CKD.

Genetic Factors

It has been noted that MeN (or CKDu) has, as yet, mainly been reported from a few areas in spite of the fact that the combination of heat exposure, long strenuous physical work and risk for repeated episodes of dehydration possibly exists in several areas of the world. Sugar cane harvesting after burning for example is common in Brazil. In spite of this MeN (or CKDu) has been reported only from some geographical areas [4]. Thus some sort of genetic predisposition has been suggested, but so far no data on this have been provided [50].

Pathology

The first detailed clinical and pathological characterization of what has been named Mesoamerican Nephropathy came in 2013. Eight sugarcane workers with CKD suspected MeN were studied. The renal morphology was evaluated with light microscopy, immunofluorescence,

and electron microscopy and showed a similar and unique morphology in all biopsies. The morphology showed extensive glomerulosclerosis (29%-78%), increased glomerular size, chronic glomerular ischemia, tubular atrophy and interstitial fibrosis. Only mild vascular changes were seen. Two of the patients showed focal segmental sclerotic lesions in the glomeruli and electron microscopy indicated podocytic injury. The included patients had eGFR 27-79 mL/min/1.73 m^2 (CKD-EPI), low levels of albuminuria, elevated levels of tubular damage biomarkers (NAG and Protein HC). Hypokalemia was frequent (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 pathogenesis [14]. López-Marín et al. [15] performed renal biopsies of 46 patients diagnosed as MeN in *El Salvador* [51]. It is important to recognize that the inclusion criteria were not the same as in Wijkström et al. [14] in this series of biopsies. Among included patients, several had proteinuria and hypertension. The main findings reported in that study were interstitial fibrosis and tubular atrophy with or without inflammatory monocyte infiltration. In addition, generalized glomerularsclerosis, 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 albeit the authors of this report concludes that the renal biopsies are more consistent with tubulo-interstitial 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 previous histopathological findings [15].

Another nineteen patients with MeN, from Nicaragua was examined in 2014 [16]. Average eGFR was 58 ml/min/1.73 m^2. Blood pressure was normal (<140/90) in all patients and the urine-albumin-creatinine ratio were normal in all but three patients. Electrolyte abnormalities were common, low sodium, magnesium and potassium. The renal morphology, which was very similar to what was previously seen in *El Salvador*, will soon be reported in detail.

Already in 2012 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 was presented [52]. Cases where selected from a screening programme which identified persons with albuminuria and many of them had hypertension and thus not identical to those examined in *El Salvador*. 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 were 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 of 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. The authors conclude the tubulo-interstitial damage to be the main pathological lesion in CKDu in Sri Lanka, albeit the morphological changes that are described emphasize also the glomerular lesions. It was suggested that environmental causes/pathogens should be further investigated to find the aetiology behind CKDu in Central Sri Lanka.

Clinical Features

Mesoamerican nephropathy typically affects relatively young and middle aged men engaged in physically demanding outdoor agricultural work in a hot climate prone to dehydration episodes [51]. In typical cases an increased concentration of creatinine is seen in plasma and a calculation of eGFR demonstrates an eGFR below 60 mL/min/1.73 m^2. The prevalence increase with age and number of years at agricultural/plantation work. Proteinuria is missing or limited and no alternative explanation for CKD such as hypertension, diabetes, infections or urogenital malformations including polycystic kidneys are found. Ultrasound examination of kidney often display somewhat small kidneys with lower than normal height of the cortex (less than 2 cm). The plasma concentration of potassium and sodium is often low, and hypokalemia is a common observation. If the CKD progresses, terminal renal disease may develop with attending symptoms, signs and biochemical changes.

Herrera et al. [51] present clinical characteristics of 46 participants selected from a screening programme in *El Salvador* [23] who were aged between 18-59 and had CKD stage 2 or 3. Poverty was the leading social determinant observed. Risk factor prevalence of various conditions and exposures were 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 on albuminuria 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. Possibly the notion of '80% macroabulinuria' is therefore not correct. Analysis of plasma showed that metabolic alkalosis (46%), hyponatremia (48%), hypocalcaemia (39%), hypokalemia (30%), and hypomagnesemia (20%) were common in this group [51].

Crowe et al. [53] examined the frequency of heat-related health effects among harvesters (n=106) exposed to occupational heat stress compared to non-harvesters (n=63). Heat and dehydration symptoms (headache, tachycardia, muscle cramps, fever, nausea, dyspnoea, dizziness, dysuria and swelling of hands or feet)) 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 [53].

Two medical students in Kidney International 2014 provide a personal presentation of the CKD epidemic in Chinandega, Nicaragua [54]. They cite information from the area reporting that 'at least 3000 people (a region in north western Nicaragua with population of around 150,000) alone have the disease' and present the almost insurmountable 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.

Diagnosis

Diagnosis of Mesoamerican nephropathy should be considered in patients with lowered GFR without common or typical risk factors of CKD such as diabetes, hypertension, signs of chronic glomerulonephritis with albuminuria and/or haematuria, infections that directly or indirectly affect the kidneys or urogenital malformation; and who have experienced long periods of physically demanding agricultural work in hot climate with the risk of becoming dehydrated. Biochemical examination will, apart from a lowered GFR, in typical cases display none or low grade

albuminuria, often elevated urine excretion of biomarkers indicative of tubular dysfunction and plasma sodium and/or potassium in the low range. Ultrasound of kidneys often will show somewhat small kidneys with a narrow cortex [51].

Differential diagnosis

Other types of endemic nephropathies should be considered; such as Balkan or Aristolochic acid nephropathy, analgesic nephropathy, cadmium and lead nephropathy and nephropathy from ochratoxin and other moulds. Exposure to metals can be assessed, and ruled out, from proper measurements in blood and/or urine. Microscopical examination of renal biopsies will also help to distinguish between different types of endemic nephropathies [55].

Prognosis

Information on the long term prognosis of patients with MeN at an early stage is largely missing. From the high incidence of ERSD and mortality in some severely affected areas of *El Salvador* and Nicaragua it is evident that the renal disease may progress. How fast and under what conditions have not, as yet, been reported.

In Sri Lanka risk factors associated with mortality in 143 patients with chronic kidney disease of uncertain aetiology were examined. Eight out of 45 patients (18% aged under 65 and with eGFR below 60 ml/min per 1.73m^2) 2003 had died within two years. Out of nine aged over 65 having an eGFR <60 ml/min per 1.73m^2 three (33%) had died. High blood pressure was a risk factor for disease progression and death in this cohort [56]. In should be noted that this cohort follow-up is not based on diagnosed MeN cases, which as a rule do not have hypertension.

Management and Prevention

The best known prevention is possibly to provide adequate hydration and limit exposure of workers to heat stress. Increased drinking of water with sufficient amounts of minerals such as sodium and potassium is recommended to minimize the effects of excessive sweating, and avoidance of NSAIDs is highly recommended. Due to risk of hypovolemia and low blood pressure during heat exposure the use of ACE inhibitors for renoprotection in cases with MeN is not generally recommended [57], albeit this has not been examined. 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 [6].

In Kidney International (2013) an attempt was made to raise the awareness that acute kidney injury (AKI) is a major global health problem resulting in millions of death 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 and other potential nephrotoxic contaminants are key elements for prevention [58].

Summary

During the last ten years it has become evident that 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 CDK 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.

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