

# Mesoamerican Nephropathy: Resolving the Enigma?

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Chronic kidney disease (CKD) is a worldwide public health problem that affects millions of people [1]. The major causes of end stage kidney disease (ESKD) are: diabetes mellitus, hypertension and chronic glomerulonephritis [1]. Other causes of CKD have also been reported, such as aging, infectious diseases, herbal nephrotoxins and local environments. Reports on kidney disease of uncertain etiology are few. Mesoamerican Nephropathy is one of them, which describes a devastating epidemic of chronic kidney disease emerged in the last decade in Central America.

This 'new endemic' kidney disease is first described among poor male sugarcane workers in the early 2000 [2] and was called 'Sugar Cane Nephropathy'. Subsequently the name Mesoamerican nephropathy has been suggested by the First International Research Workshop in November 2012 based on the area where was first characterized [3]. In this entity the occurrence of CKD was not associated with the conventional risk factors. Younger population and farmers were independently associated with CKD and men were more vulnerable than women [4].

Concerning Mesoamerican nephropathy some similarities with Balkan endemic nephropathy were observed. Both diseases are reported in male farming populations, with absence of anemia and inflammatory responses in kidney tissues, as well as absence of uroepithelial tumors among affected patients, while evidence of an underlying tubulointerstitial pathology is present [5]. Long-term consumption of food contaminated with aristolochic acid underlies Balkan endemic nephropathy pathogenesis [5]. In this issue of the journal, Elinder CG et al. in their extensive review [6] clearly present the more recent information for this new entity.

In the past decades concerns were raised over the rising number of CKD prevalence in certain areas of El Salvador [7], Nicaragua [8-10] and Sri Lanka [11]. The phenomenon firstly drew attention when a high percentage of young agricultural workers started dialysis without an obvious cause and clear etiology of CKD. Subsequently a number of published studies in collaboration with a local team of researchers confirm the problem [7-11]. In El Salvador, in young individuals aged 20-60 years, particularly men, a high prevalence of decreased kidney function of unknown origin has been reported. The adjusted ORs of decreased kidney function for 10-year increments of coastal sugarcane or cotton plantation work were 3.1 (95% CI, 2.0-5.0) in men and 2.3 (95% CI, 1.4-3.7) in women [7]. In addition, in Northwest Nicaragua the same aging populations 20-60 years exhibited a high prevalence of decreased kidney function of unknown origin [8]. Furthermore, in another area of Nicaragua, in Quezalguaque, in a population-based prevalence study including 1882 eligible households, CKD was common, particularly in younger men, with features most consistent with tubulointerstitial disease [9]. The high prevalence of CKD was not linked to traditional risk factors, and the authors suggested that it may be associated instead with occupational exposure to heat stress in conjunction with pesticide

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inhalation, sugarcane chewing and sugar intake during the workday [10]. Additionally, in other studies in populations of Sri Lanka characteristics of CKD of uncertain etiology were also noticed [11].

The Mesoamerican nephropathy was initially present in young male agricultural workers from communities along the Pacific coast mainly in people engaged in sugarcane cultivation, but later the disease was also reported in other types of farming. On the basis of the clinical profile these patients usually present with various degrees of nephropathy and progressive kidney failure, with normal or mildly elevated systemic blood pressure, without other potential common risk factors, such as diabetes mellitus and/or obesity [12]. Patients usually have no hematuria, while proteinuria is absent or of non-nephrotic range, and often patients exhibit hyperuricemia and or hypokalemia [12].

The cause of Mesoamerican nephropathy remains uncertain, however considerable efforts have been made to elucidate the cause, or causes, of this endemically observed CKD. The disease may be linked to multiple factors, including diet as well as environmental and occupational exposures. A growing body of evidence indicates that the causative pathway should be the repeated episodes of dehydration due to heavy physical labor in a hot climate along with occupational heat stress and water and solute loss [3]. In multiple studies recurrent loss of sodium and potassium is suggested, a condition that possibly plays a significant role [12] and has been proposed as one of the causes of the repeated injury to proximal tubules which could lead to global glomerular sclerosis [13].

Other potential risk factors that should be taken into consideration are occupational exposure to pesticides that frequently used during sugarcane and cotton production. Furthermore, other potential causes include the frequent intake of analgesic drugs and nephrotoxic medication and/or infections, such as leptospirosis. However, little evidence has come forth supporting the contention that exposure to agrochemicals, pesticides, heavy metals, and drugs or locally occurring infections are causative for Mesoamerican nephropathy [3]. On the other hand, it is important to point out that the changes might be aggravated further by dehydration and subsequent activation of the renin-angiotensin-aldosterone system, since the plantation workers operate in extremely hot areas [3,10]. To elucidate the etiology of the disease, various factors need to be accounted with multi-country studies and a prospective cohort design including genetic, experimental, and mechanistic methods.

The disease is presented with specific histopathological changes in kidney biopsy analysis. The low urine proteinuria without active sediment is indicative of a likely tubular lesion rather than a glomerular lesion. However, the light microscopic findings indicate both tubulointerstitial, and glomerular damage showing chronic tubulointerstitial disease with varying degrees of tubular atrophy, essentially proportional to the stage of CKD coupled with associated

non-specific glomerular damage, secondary glomerulosclerosis and some signs of glomerular ischemia [12].

It is therefore possible that the disease has a slow progression with a minimum urine proteinuria without active sediment. Reliable information for long term prognosis of this entity is not available. In addition a specific treatment cannot be indicated unless of supportive care and general approach of CKD prevention.

Awareness of the problems regarding the CKD and the subsequent increased morbidity and mortality have been emerging for several years among local health professionals and inhabitants [2]. However, prevention of the disease is still not carried out satisfactorily. Critical steps and characterization of social and working conditions are needed in an effort to control or eliminate the disease burden. Measurements of workload and heat, as well as water and solute loss among workers are especially indicated. Quantification of potential nephrotoxic agents in drinking water and food at the individual's residence, the reduction of events, such as dehydration and strenuous exercise as well as the use of biomarkers of early kidney injury to explore potential causes of Mesoamerican nephropathy are required. Additionally methods for valid data collection of exposures and personal risk factors in a registry and proper evaluation of biological and demographic data are also indicated. The underlying review constitutes a detailed clinical and morphologic description of this kidney disease.

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