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## Research Article

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### Epidemic Chronic Kidney Disease (CKD) in Central America: A Review of Mesoamerican Nephropathy (MeN)

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## Abstract

**Aim:** Provision of information to the interested clinician and/or epidemiologist regarding an underappreciated etiology of Acute Kidney Injury (AKI) and progressive Chronic Kidney Disease (CKD) endemic to regions of coastal Central America

**Background:** Mesoamerican Nephropathy (MeN) is a distinct clinical etiology of AKI and progressive CKD with a regional predilection for multiple areas of coastal Central America, characterized by episodic AKI with evidence of volume depletion, systemic inflammation (with or without associated Non-Steroidal Anti-Inflammatory Drug [NSAID] use) and pathologic evidence of glomerular ischemia, acute and chronic tubular injury with evidence of oxidative stress.

**Design:** Retrospective structured literature review with clinical and pathological correlations

**Method:** Structured search of the published medical literature over the last ten years was performed using pertinent PubMed Medical Subject Headings (MeSH) terms. Articles were chosen for their regional specificity, clinical relevance and pathophysiological correlations for the population of interest.

**Conclusion:** Mesoamerican Nephropathy (MeN), as an important and underappreciated etiology of both endemic AKI and progressive CKD, remains an unusual and relatively newly discovered cause of kidney-related morbidity and mortality among the largely rural, medically underserved and otherwise vulnerable populations of Central America. Further prospective study of both the specific epidemiologic characteristics of the disease and the specific pathophysiological mechanisms in play appear long overdue.

**Keywords:** Kidney failure in Central America; NSAID-associated CKD; Oxidative stress in renal disease; Regional etiologies of ischemic AKI

## Introduction

Mesoamerican nephropathy is an important yet currently poorly understood cause of acute and chronic kidney failure, endemic to certain coastal areas of Central America. While components of volume depletion, acute tubular necrosis and systemic inflammation appear to be operable, the distinct etiologic trigger(s) remain(s) obscure, requiring further study for elucidation.

With the progressive nature of medical knowledge moving in parallel to the timeline of our somewhat frail human history, it is indeed increasingly unusual for the physician/scientist to find something actually “New” in the world. With such occurrences, one does well to sit up and take notice of both how far we have come, as well as to take inventory of how far we may have to go. This is particularly true when the causes and effects of a disease process, particularly one of clinical importance, remain cryptic despite vigorous epidemiologic and other investigation.

In this case, a major medical “Whodunit” has for the last two decades been unfolding before the eyes of the public health and nephrology communities in Central America. This disease process, a newly recognized form of progressive Chronic Kidney Disease (CKD) leading to increasing morbidity, disability and death, has been termed Mesoamerican Nephropathy (MeN).

The recognition of MeN as a distinct clinical entity arose out of the collective observations of Internal Medicine and Nephrology specialists in El Salvador noting that a high percentage of patients initiated on dialysis in El Salvador had no obvious cause of CKD [1]. In one study of such unfortunate patients, the cause of end-stage renal disease (ESRD) was known in only 70 of 205 (34%) of those hospitalized. Several subsequently published studies revealed a similarly high percentage of CKD of unclear etiology in various regions of Nicaragua, Guatemala and Costa Rica, giving rise to the name “Mesoamerican nephropathy” (from the Greek *mesos*, meaning “Middle”).

Kidney disease of all causation in Central America has been a growing problem for the last two decades. For those patients requiring dialysis or transplantation, referred to collectively as Renal Replacement Therapy (RRT), the prevalence increased from 119 patients per million population (ppm) in 1991 to 660 ppm in 2010. The kidney transplant rate alone increased from 3.7 ppm in 1987 to 6.9 ppm in 1991 and to 19.1 ppm in 2010, with diabetes continuing as the leading cause of ESRD [2]. However, the recent increase in diagnosed renal disease does not appear referable to the usual causes of diabetes and hypertension, as the incidence of these maladies has remained substantially unchanged over the period of study. In comparison to a more global picture of kidney disease prevalence and incidence, for men aged 50 to 54 years, the CKD-associated mortality rate in Nicaragua and El Salvador between 2000 and 2009 was approximately 110/100,000 population, compared with less than 40/100,000 in countries such as Panama and Cuba, with an incidence of new cases of previously undiagnosed CKD at 13% in comparison to 5% in the United States [3].

The natural history of renal disease specific to Central America is somewhat difficult to characterize as much of the rural population has somewhat limited access to healthcare providers for diagnostic purposes and to healthcare in general. At the same time, the largely agrarian populace, placing a high importance on the ability of particularly its male population to work, remains reticent to seek healthcare or to assume the “Sick Patient” role. The initial signs and symptoms of kidney disease, which may include only increasing fatigue, episodic weakness, muscle cramps, mild SOB, decreasing appetite and nausea remain are somewhat nondescript and likely explain the reason that many patients are not seen until significantly advanced in their disease process or at the time of their mortal event [4].

Once the above noted studies and attendant statistics were appreciated by the public health community, epidemiologic studies were instituted to further characterize MeN as a disease process and to establish a causative etiology, although the working definition of “CKD in young, agricultural workers in Central America in the absence of any other clear etiology” has been generally accepted [3]. Regardless of definition, it remains clear that the region faces a new and clinically important disease process of “Epidemic” proportion and one that remains a significant public health menace for the whole of Central America.

Several important demographic and geographic distinctions have come to light in the epidemiologic studies of MeN. Of particular interest is the predilection of affected patients to live in lower altitude, coastal regions of Nicaragua, El Salvador and Costa Rica (17-19%), particularly in deference to the lower incidence (2%) noted in their mountain dwelling compatriots; in addition, there appears to be an increased incidence in agricultural versus non-agricultural workers [5]. The reasons for these differences remain somewhat cryptic; however, potential mechanisms have been proposed.

A multiplicity of putative risk factors for MeN have been suggested, including agricultural and physically demanding work in a hot climate, specifically Central America, exposure to pesticides, excessive use of Nonsteroidal Anti-Inflammatory Agents (NSAIDs), age greater than 60 years, male sex, low body mass, consumption of sugar-containing rehydration drinks and lower socioeconomic class or poverty [6,7]. Indeed, in nearly all studies, male patients outnumber females from 3 to 5:1 and the most important underlying risk factor for MeN appears to be hard, physical work in excessively hot climates [3].

Diagnosis of MeN (and the lack thereof), in those at highest risk, is also known to have a very strong cultural component in the generally impoverished, agricultural nations of Central America. Manual labor, especially as it pertains to agricultural pursuits, is an important facet of everyday life, not only from the standpoint of perceived communal worth, but as necessitated by the widespread poverty seen there and the absolute need for a man to physically provide for his family. Jobs, particularly “Good” jobs are not always easy to come by and with the high standard placed on men based on their ability to perform, as well as a shunning of the “Sick Patient” role, people work because they must and usually far beyond their normal capacities. In this environment, symptoms are minimized, ignored and only in cases of complete incapacitation would one not labor long and hard. The recognized association between MeN and hard, physical labor in a warm climate (usually cutting and processing sugar cane or working on cotton plantations) is a recurrent theme and the physiologic “Heat Stress” associated with the attendant high temperatures apparently predispose to development of the syndrome [8]. By way of example, the average temperature at which the United States Occupational Health and Safety Administration (OSHA) recommends only 15 minutes of work per hour is usually reached during the dry sugarcane harvesting season by 9:15 AM in Costa Rica; however, the average sugarcane cutter works for multiple more hours to secure their needed income, typically based on the amount of cane harvested [9].

The exact pathogenesis of MeN is not known with certainty, although it is postulated that the most likely cause is repeated episodes of Acute Kidney Injury (AKI) related to dehydration, loss of minerals, hypovolemia sometimes accompanied by rhabdomyolysis (acute muscle cell breakdown, the byproducts of which are toxic to the kidneys), systemic inflammation, use of NSAIDS and oxidative injury [1,9].

Clinical features leading to the diagnosis of MeN include weakness and arthralgia and/or muscle cramps, which may lead to excessive self-dosing with NSAIDs. Other nonspecific symptoms include headache, tachycardia, fever, nausea, difficulty breathing, dizziness, swelling of the hands/feet and dysuria, which may be described as occurring weekly, particularly among harvesters. Laboratory features reveal an increased serum creatinine, usually benign urinary sediment without evidence of hematuria or proteinuria, as well as plasma concentrations of sodium, potassium and magnesium that are often low with mildly elevated uric acid [8]. Ultrasound examination of the kidneys show somewhat small kidneys with decreased cortical thickness; both findings entirely consistent with CKD of almost any cause [4].

Pathologic evaluation of the kidney tissue by histology shows prominent tubular atrophy and fibrosis, as well as chronic glomerular changes, including glomerulosclerosis and hypertrophy of the glomerular tufts. Chronic glomerular ischemia is also suggested by the wrinkling of glomerular capillaries and thickening of Bowman's capsule. Some increase in mesangial matrix may be seen without mesangial cell proliferation. Occasionally an inflammatory monocyte infiltration is seen [10,11]. Diagnostically, serologic and urinary studies are carried out to rule out other forms of CKD (in the absence of obvious risk factors) and in a large number of cases, percutaneous renal biopsy is performed to seal the diagnosis and rule out any other form of endemic nephropathy.

In consideration of the diagnostic and therapeutic modalities available, healthcare screening as a function of everyday life for the general, primarily agrarian, population of Central America simply does not occur. It follows then that most of the population at risk would not receive any type of intervention until they have become symptomatic. Unfortunately, in the case of both acute and/or chronic kidney disease, some component of irreversible damage is already highly likely by the time of symptom occurrence. This is particularly true of more clinically occult processes that cause episodic acute dysfunction and apparently resolve by the patient's accounting, but which may leave residual scarring of the kidneys and slowly progressive destruction of the functioning renal mass [12]. Potential strategies to counter this common pathophysiology pathway will be discussed.

There is no specific treatment of MeN. Therapeutic modalities in MeN, and indeed in most forms of progressive CKD focus on preventing further dysfunction once disease is discovered, as there is little active therapy for chronic progression besides the control of volume status and other exacerbating factors, such as hypertension, diabetes and hyperlipidemia. Therefore, treatment is largely supportive in nature with avoidance of the severe heat exposure felt to be optimal, along with adequate hydration therapy with electrolyte-containing fluids. In some cases, the avoidance of fructose-containing fluids has been advocated, although the hard data to support this posture is somewhat lacking. In addition, exposure to pesticides should be avoided, although this is advisement regarding general health, as these agents, in and of themselves, do not appear to be nephrotoxic [3,12].

From a pharmacological standpoint, it is noteworthy that Angiotensin-Converting Enzyme Inhibitors (ACEI), as well as Angiotensin Receptor Blockers (ARBs), both of which are usually mainstays of antihypertensive therapy and felt to confer protective effects against the progression of many forms of renal disease, should not be used in the treatment of MeN patients. Since hypovolemia and relative renal hypoperfusion may be pathogenetic in this disease process, it is felt likely that blockade of the Renin-Angiotensin System (RAS) may predispose individuals to AKI in such a setting, thus increasing the risk of MeN [11].

There is little data on the long-term prognosis of patients with MeN when it is detected at an early stage and while it is evident that the renal disease may progress, the rate of progression is not well described. It is known that MeN is associated with a high mortality rate, although this appears to have much more to do with its prevalence in regions where RRT is often not readily affordable or even available. However, the number of patients on Hemodialysis (HD), Peritoneal Dialysis (PD) and status post-transplant have been growing steadily as more patients reach ESRD status [1]. It would appear likely, particularly from a geographic and demographic standpoint, that PD might be one of the best ways to care for the largely agrarian and rurally dispersed population; however, the necessity of a strictly clean environment to perform this home therapy may make its widespread use impractical.

Since the disease process usually comes to medical attention late, inflicting significant damage on a large segment of the working population, and since there are no great means to care for the population at risk once CKD (and/or ESRD) develops, the crucial question that remains is what can actually be done? It appears the simple, yet profound key to dealing with the public health epidemic of MeN is *primary prevention*.

One of the major points of emphasis in the avoidance of MeN would be avoidance and/or minimization of the exposure to the excessive heat stress that appears to be one of its most potent triggers. One of the most effective means to achieve this end might be a type of mandatory governmental registration of sugar cane and cotton plantation workers whereby employers would be required to monitor and regulate the number of hours worked per day and per week, with requirements to spot check the urine specific gravity of workers as an inexpensive way to monitor hydration status and/or to shift field work away from the hottest part of the day to either earlier mornings or evenings in order to minimize the heat stress factor. If employers were required to show compliance with this program to sell their products in the marketplace, much of the patient risk could likely be avoided for a reasonable amount of overhead expense. Making “Cooling Stations” available to be used every 2-3 hours for a 20-minute period close to the location of the field work, as are available in many large cities during times of heat stress, would also be a potentially practical way to avoid kidney damage in the field worker population.

The monitoring of workers’ use of alcohol, fructose-containing rehydration drinks and NSAIDs, all felt to be at least potential risk factors for development of disease, could be addressed by mandatory worker health education about MeN and its risk factors, the availability of acetaminophen for muscle complaints, as well as glucose and electrolyte-based rehydration therapy made available to workers in the field.

To understand the challenges to effective health care change in an area like Central America, it is important to know the other major health problems of the area and how the current health care system is structured to meet the challenges that exist. Maternal and child health access inequity continues to be a significant problem in this largely rural, agriculturally based area of the world. Other health problems which exist, primarily as a result of other global influences, include alcoholism, ongoing smoking and smokeless tobacco use, as well as the burgeoning number of chronic medical conditions of Westernization, namely cardiovascular disease, hypertension, hyperlipidemia, obesity and diabetes. Many areas continue to struggle with basic needs for clean water and adequate sanitation practices to keep the general population healthy. Challenges in social development also exist, such as employment inequality, informal employment, lack of universal access to education and the difficulty of empowering and protecting women in a male-dominant agrarian society. The health care system, as it exists in the nations of Central America, especially outside the major metropolitan areas, is rudimentary at best and somewhat disjointed, suffering primarily from the dispersion of a largely rural population and somewhat challenging geography. Funding for health care is an understandably lower priority in nations where poverty is so much the norm. One can see with the current slate of ongoing public health issues and systems in place, why kidney disease in one subset of the population might be a lower priority, despite the productivity losses and additional societal costs of long-term disability in these patients [13].

The problems of informal employment and the significant premium placed on the ability of the man in Central America to work without complaining would definitely be significant cultural hurdles to overcome in calling sugar cane and cotton producers into accountability for the health of their hirelings and would likely require some financial incentives and/or governmental intervention and authority to make these a reality. The economic impact of health interventions for those potentially threatened by MeN would likely not be significant to the large-scale employers to assimilate into their work practices. However, the impact on the individual families of Central America would likely be more significant, in that the income produced by working male family members is usually all that keeps them from the brink of austere poverty. One means of helping to prevent this would be strict monitoring of the hiring practices of large employers with universally mandated compliance to assure workers are not discriminated against for following the guidelines of healthy work practices.

To date, little research has been done regarding the efficacy of any novel therapeutic interventions or active therapies for MeN, primarily because the disease is usually discovered late in its course and not that much is yet known about the natural history of untreated disease [14]. There are, however some theoretical considerations of the apparent mechanisms of disease progression which may lend themselves to intervention. Since pathologically there appears to be a significant component of interstitial change with tubular atrophy and fibrosis consistent with so-called interstitial nephritis (a type of “Allergic” response within the kidney which can sometimes be seen with NSAID use), the use of corticosteroids with their strong anti-inflammatory effects, at least early in the course of disease, might well be efficacious [4,12]. This could fairly easily be studied in a stratified, double-blinded manner based on the changes initially present, compared to those seen on follow-up kidney biopsy; a very objective study vehicle.

In addition, the primarily male predilection of MeN would make testing for a genetic marker, or possibly a sex-linked carrier state, a potentially profitable field of study. This would allow the follow-up of only those patients which had evidence of the genetic predisposition for MeN and would make screening and treatment modalities more economically feasible and easier to rationalize for both employers and the general populace.

Targets for further epidemiologic study in this poorly understood malady include expansion of risk factor consideration, study of other areas of heat stress-induced renal dysfunction (i.e., that of Sri Lanka, where a similar disease process is beginning to be reported) and genetic testing to determine markers in susceptible populations.

Further preventive public health intervention opportunities do exist, primarily in the areas of raising awareness of MeN in the general population of Central America, and specifically the education of cane and cotton plantation owners and at-risk workers regarding risk factor avoidance, regarding the signs and symptoms of kidney disease, as well as the importance of early detection and treatment. In addition, the problem is already receiving attention at the national and regional governmental levels as a potentially preventable public health malady. However, cohesive national “Plans of attack” with specific recommendations and plans of implementation, including the governmental ability to enforce rules and regulations at the plantation level with economic leverage in the marketplace are slow in coming and at the present, still lacking [14].

In summary, Mesoamerican nephropathy remains a medically interesting, socially and politically charged and clinically challenging disease process, specific at this time to the nations of Central America. Primary prevention of the malady needs to continue to be vigorously pursued in the endemic areas at risk. Going forward, further epidemiologic study and aggressive clinical and public health intervention, including population-based public health educational initiatives must continue to be advanced to protect the population of those at risk from this important epidemic, currently the “New kid on the block” in the world of kidney disease.

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