

# Mesoamerican Nephropathy or Global Warming Nephropathy?

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## Key Words

Chronic kidney disease · Mesoamerican nephropathy · Sugarcane · Uric acid · Global warming

## Abstract

**Background:** An epidemic of chronic kidney disease (CKD) of unknown cause has emerged along the Pacific Coast of 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. Renal biopsies show chronic tubulointerstitial disease. While the cause remains unknown, recent studies suggest that it is driven by recurrent dehydration in the hot climate. Potential mechanisms include the development of hyperosmolarity with the activation of the aldose reductase-fructokinase pathway in the proximal tubule leading to local injury and inflammation, and the possibility that renal injury may be the consequence of repeated uricosuria and urate crystal formation as a consequence of both increased generation and urinary concentration, similar to a chronic tumor lysis syndrome. The epidemic is postulated to be increasing due to the effects of global warming.

**Summary:** An epidemic of CKD has led to the death of more

than 20,000 lives in Central America. The cause is unknown, but appears to be due to recurrent dehydration. Potential mechanisms for injury are renal damage as a consequence of recurrent hyperosmolarity and/or injury to the tubules from repeated episodes of uricosuria. **Key Messages:** The epidemic of CKD in Mesoamerica may be due to chronic recurrent dehydration as a consequence of global warming and working conditions. This entity may be one of the first major diseases attributed to climate change and the greenhouse effect.

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An epidemic of chronic kidney disease (CKD) of unknown etiology is occurring in Central America, primarily along the Pacific Coasts. First described in 2002 [1], it likely has been present since the early 1970s, but has increased markedly over the last 2 decades [2]. To date, there have been nearly 20,000 deaths, in part because most of the victims do not have access to dialysis [3].

Clinically, the disease presents primarily in men working manually in the sugarcane fields, but it has also been observed in other groups that work manually outdoors, such as construction workers, subsistence farmers, and other similar groups of people. Most of the subjects are as-

ymptomatic until they start developing signs of uremia [4]. However, there is evidence that the disease has been slowly progressive, beginning with an asymptomatic rise in serum creatinine, in association with low grade or absent proteinuria with occasional red cells and white cells present in the urine sediment. However, some subjects complain of 'sandy urine' that causes dysuria, although uninfected when tested by urine culture [5]. Blood pressure may be slightly high, but not at levels (>160 mm Hg) commonly associated with renal progression. Most strikingly, the disease does not appear to be due to any of the common causes of end-stage renal disease, such as diabetes, hypertension, glomerulonephritis, or polycystic kidney disease. Thus, the disease has been called 'Mesoamerican Nephropathy', and is thought to be a new form of kidney disease [4, 6].

There has been much effort to identify the cause of the disease. Renal biopsies, when performed, show a chronic tubulointerstitial disease with focal inflammation, and with signs of glomerular ischemia and secondary glomerulosclerosis [7]. The recognition that this is primarily a chronic tubulointerstitial disease has raised the possibility that toxic metals might be involved in the etiology, such as lead, cadmium, arsenic – however, to date the preliminary studies performed do not support these as a cause. Silica released from burned sugarcane remains a possibility, but it does not explain why the disease is also observed in other groups. Likewise, while some studies have focused on agrichemicals and pesticides, no specific pesticide has been identified, and furthermore it does not explain the presence of this disease in other groups. Likewise, infections such as leptospirosis and Hanta virus have been considered, but clinical manifestations of these diseases are largely lacking.

### **The Role of Dehydration as a Cause of Mesoamerican Nephropathy**

One common characteristic to all groups developing this disease, however, is recurrent dehydration occurring during heavy work in the hot environment [5, 8–10]. Indeed, some studies have shown that the disease is more common in workers in sugarcane fields that are at a lower altitude, compared to those at a higher altitude, where the temperature is less hot. Workers start early in the morning before the day gets too hot, but studies have shown that the heat indexes cross into the unsafe zone, defined by the Occupational Safety and Health Administration, well before 10:00 in the morning, while workers continue cutting cane for several more hours on a typical

day [8]. As such, many of the workers develop signs of dehydration during the day (fainting, light headed, jittery), heat strokes are often confused with fever, dysuria is frequent, and urine analyses show signs of urinary concentration (elevated specific gravity, elevated urine osmolality) at the end of the workday [5, 8–10]. This happens cyclically, as a on a daily basis.

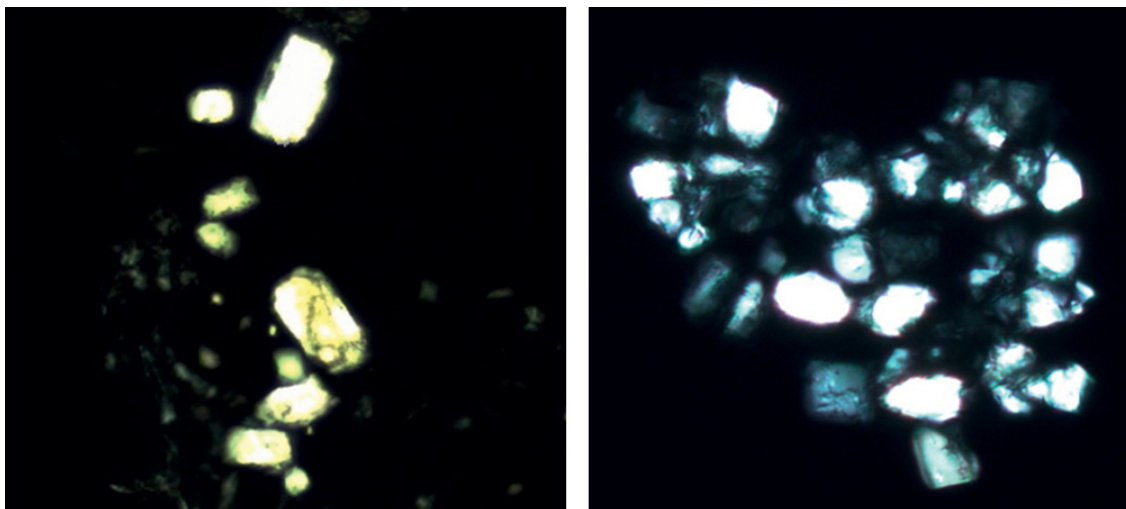
#### *An Animal Model of Dehydration Associated CKD*

Historically, dehydration (loss of water) and volume depletion (salt loss) are thought to result in 'pre-renal' kidney disease, in which no frank injury occurs unless blood pressure and renal blood flow drop to levels that cause acute tubular necrosis. However, we recently developed an animal model of recurrent dehydration associated with heat exposure in mice. As a remarkable finding, these mice developed impaired renal function and tubulointerstitial fibrosis after 5 weeks [11]. Interestingly enough, the timing of hydration was key; indeed, if hydration was provided immediately after each cycle of dehydration, renal injury was prevented, whereas if the same total amount of hydration was provided until the end of the day, renal injury ensued. This study thus suggests that adequate hydration needs to be provided to the sugarcane workers while they are in the fields, not afterwards.

The mechanism by which the kidney injury was developing was also explored. The mice lost salt and water by sweating in their feet, so they tended to become hyperosmolar during the day and this activated an enzyme system (aldose reductase-sorbitol dehydrogenase-fructokinase) in the proximal tubules. This enzyme system converts the glucose being reabsorbed in the proximal tubule to fructose, which is then metabolized by fructokinase to generate oxidants and uric acid that causes local tubular injury. Interestingly, when mice lacking fructokinase were recurrently dehydrated, they were protected from kidney damage [11].

### **New Insights into Kidney Injury**

Recently, our group identified a potentially more important mechanism to account for the development of Mesoamerican nephropathy. Specifically, exercise under heat stress is known to cause subclinical rhabdomyolysis that is associated with the release of nucleotides and a rise in serum uric acid [12, 13]. Indeed, hyperuricemia is very common among the sugarcane workers, and serum uric acid increases during the work day [9]. In turn, during the day, dehydration leads to urinary concentration and acidification, thereby resulting in high urinary uric acid con-



**Fig. 1.** Urine sediment from a sugarcane worker in Nicaragua. The urine uric acid crystals are box-like and negatively birefringent.

centrations that can exceed solubility. Urate crystals are common in the urinary sediment of sugarcane workers (fig. 1). Indeed, we found that many of the sugarcane workers develop urine uric acid levels greater than 100 mg/dl per day, which is similar to that observed in subjects suffering from acute kidney injury following chemotherapy (tumor lysis syndrome) [14]. Thus, we have proposed that the Mesoamerican nephropathy may be caused by repeated episodes of hyperuricosuria and urate crystal formation that occurs through hard work on hot days when hydration is limited or delayed.

### Why the Epidemic?

The last century has seen a progressive rise in temperatures, with acceleration in the last 20 years. While the absolute increase in temperature is relatively subtle (0.8 degrees Celsius), this has led to a dramatic increase in exceptionally hot days. Indeed, studies show that 75 percent of extremely hot days (exceeding the 99th percentile) are currently attributable to global warming [15]. As an example, in the summer of 2015, there was a major heat wave in Karachi with over 40,000 people suffering from heat stroke, and another heat wave in Iran where the ambient temperature crossed 160 degrees Fahrenheit [16, 17]. For those subjects working daily in the sugarcane fields extremely hot days are common [9], and the intensity of the work adds up to further increase body core temperature.

It is interesting that epidemics of CKD are now being reported in multiple countries, primarily in the tropics, including India, Bangladesh, Sri Lanka, Egypt, Mexico and Central America. A common theme is that the CKD is occurring in subjects working manually outside, directly exposed to sunshine, frequently in areas where there is significant water shortage or scarce access to potable water. In conclusion, we propose that the Mesoamerican nephropathy is essentially a consequence of global warming, and may be one of the first major diseases described as a consequence of extensive fossil fuel use and the greenhouse effect.

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