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ABSTRACT

Increase in the prevalence of chronic kidney disease (CKD) is observed in Central America, Sri Lanka and other tropical countries. It is named chronic interstitial nephritis in agricultural communities (CINAC). CINAC is defined as a form of CKD that affects mainly young men, occasionally women. Its aetiology is not linked to diabetes, hypertension, glomerulopathies or other known causes. 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. Although the aetiology of CINAC is unclear, it appears to be multifactorial. Two hypotheses emphasizing 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, Cuba and Myanmar where agrochemicals are sparsely used; the mosaic geographical pattern in CINAC endemic areas; the presence of CINAC among women, children and adolescents who are not exposed to the harsh working conditions; and the observed extra renal manifestations of CINAC. 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.

Keywords: chronic interstitial nephritis in agricultural communities, CINAC, dehydration, heat stress, herbicides

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with increasing prevalence and incidence, high cost and adverse outcomes such as vascular disease and premature death. Given the limited access to health services including availability of renal replacement therapy in the low and mid income countries (LMIC), advanced stages of CKD mean death over a short time period in most cases. Well-known causative factors of CKD include mainly diabetes, hypertension and well-characterized renal syndromes [1]. In addition to these ‘traditional’ causes, glomerular and tubulo-interstitial diseases due to infections, nephrotoxic drugs, herbal medications, and environmental and occupational exposure to toxicants contribute substantially to CKD, particularly in LMIC.
Since the early 1990s, coinciding with a more productive and extensive exploitation of land for agriculture [2], an increase in CKD prevalence related to non-traditional risk factors primarily affecting male agricultural workers has been reported in several tropical countries: El Salvador, Nicaragua, Guatemala and Costa Rica in Central America, Sri Lanka and India in Asia, and Egypt in Africa [3, 4]. This review reflects the opinion of a group of clinical and public health academics, involved in conducting research on the problem of chronic interstitial nephritis in agricultural communities (CINAC) in the two areas where the disease is highly prevalent, i.e. Sri Lanka and Central America.

Classic presentations of CINAC in both locations are in young men, between the third and fifth decades of life, mostly agricultural workers such as: paddy farmers in Sri Lanka and India and labourers working in sugarcane or general crops in Central America. However, there are many CINAC cases among non-agricultural workers, including women and children who live in the same environment. Another important fact is that in both regions these agricultural activities are conducted at low altitudes with high humidity and temperatures characteristic of a tropical climate. Indeed, this is the type of land where rice and sugarcane has been cultivated for centuries.

Different terms have been used to describe CINAC in the medical literature: chronic kidney disease of unknown origin; chronic kidney disease of uncertain origin; chronic kidney disease of unknown aetiology; agrochemical nephropathy, etc. In some cases, the disease is named after the region or country of its origin: Central American nephropathy; Salvadoran agricultural nephropathy; Mesoamerican endemic nephropathy (MeN); chronic tubulo-interstitial kidney disease of Central America; Uddanam endemic nephropathy (India); or Sri Lankan agricultural nephropathy, etc.

Twenty years after the reporting of the first case, CINAC is the most significant public health issue in the North Central Province (NCP) in Sri Lanka with more than 60 000 estimated patients and more than 20000 deaths annually [5, 6]. The disease is spreading at an epidemic scale to other adjacent farming areas in the Northern, Eastern, North Western and Uva provinces. The affected area covers almost one-third of the country. It is important to note that only very few patients have been reported from the Northern province of Sri Lanka, which shares similar conditions including soil, climate, agriculture and occupational patterns with the other CINAC endemic regions. The available CINAC statistics based upon hospital records show a steady increase of cases from 2000 to 2015 [7]. The underlying cause of renal failure was not identified in 82% of CKD patients seen in the renal clinic at Anuradhapura teaching hospital between 2000 and 2002 [8]. According to the NCP statistics from 2009 to 2011, aetiology is unknown in 2809 (70.2%) of the newly diagnosed CKD patients, and only 15.7% and 9.6% were diagnosed as patients with hypertension and diabetes, respectively. The male to female ratio was 2.6:1. The majority of patients with unknown aetiology (more explicit with CINAC) were already in stage 4 (40%) at presentation; 31.8 and 4.5% were respectively in stage 3 and stage 5. Patients with stage 1 and 2 accounted for only 3.4% [9]. The World Health Organization (WHO) study group (non-randomized sample) reported that the age-standardized prevalence of CINAC is slightly higher in women 16.9% [95% confidence interval (CI) 15.5–18.3] than in men 12.9% (95% CI 11.5–14.4), but noted that more advanced stages of CINAC were seen more frequently in men (stage 3, men 23.2% and women 7.4%; stage 4 men 22% and women 7.3%) [10]. This is compatible with the well-known higher prevalence of advanced stages of CKD among men as observed in many studies [11, 12].

An epidemic of CKD, not associated with the traditional risk factors, has been reported in a few coastal areas in Andhra Pradesh, South Eastern India. More than 4000 cases have already been diagnosed among paddy and coconut farmers (Dr Ganghadar, Nephrologist, Nizam’s Institute Of Medical Sciences, Hyderabad, India, personal communication).

In Central America growing numbers of CKD patients and increased CKD mortality have been observed over the last two decades, particularly in Nicaragua and El Salvador. The Pan American Health Organization has reported the following CKD-specific mortality rates (per 100 000 population) in the region: Nicaragua: 42.8; El Salvador: 41.9; Guatemala: 13.6; Panama: 12.3 [13]. These figures represent four times the global CKD mortality rate, and up to 17 times when compared with the lowest CKD mortality reported in the America region. Mortality rates of CKD are three times higher in men than in women. However, in the most affected countries, El Salvador and Nicaragua, mortality in women was significantly higher than their counterparts elsewhere in the Americas.

In El Salvador farming communities, the prevalence of CKD among adults is 15–21%. In these patients, less than half have diabetes or hypertension, males predominate, and renal damage begins early in life. CKD is the fifth leading cause of death nationwide in persons aged over 18 years and the second leading cause of death overall in men. In 2009, prevalence of renal replacement therapy was 566 per million population. According to the Ministry of Health’s 2011–2012 annual report in El Salvador, end-stage renal disease (CKD stages 3–5) was the third leading cause of hospital deaths in adults of both sexes, with an in-hospital case fatality rate of 12.6% [14]. Markers of kidney damage were found even in children living in agricultural communities [15]. Women, men, adolescents and children who live in these farming communities are affected, irrespective of whether they work in the fields or not.

**CINAC DEFINITION**

CINAC is a CKD affecting mainly young men, occasionally women and adolescents; its aetiology is not linked to diabetes, hypertension, glomerulopathies or other known causes of renal diseases. The affected subjects live and work in agricultural communities located in CINAC endemic areas with particular socio-economic-occupational determinants such as hot tropical climates with poverty, and exposure to toxic agrochemicals through work or by ingestion of contaminated food and water or by inhalation. Proteinuria is absent or low; kidneys are small with irregular contours in CKD stages 3–4 with tubulo-interstitial lesions and glomerulosclerosis at renal biopsy. However, renal biopsy is not diagnostic but contributes currently to excluding any form of progressive glomerulonephritis.

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**NDT PERSPECTIVES**

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Amyloidosis, etc. It gives an idea of the degree of fibrosis and helps in defining the prognosis of the CKD (Table 1).

### CLINICAL PROFILE

The clinical picture of CINAC identified in both Sri Lanka and El Salvador is very similar (Table 2). CINAC is a disease that progresses slowly, however at a differing pace depending on the degree of exposure to herbicides/agrochemicals and or contaminated water. The majority of patients are asymptomatic during the early stages of the disease [16]. Some of the general symptoms reported at early stages are arthralgia, asthenia, decreased libido, muscle cramps and faintness [17]. Nocturia, dysuria, post-void dribbling, urinary hesitancy and foamy urine are also reported. These symptoms appear in CKD stage 2 and tend to increase as the disease progresses. As for markers of renal damage, the urine sediment shows no significant abnormalities. Proteinuria is rare and moderate if present and can be defined as ‘tubular’ since β2-microglobulin and other tubular markers are elevated in the urine. Renal function tests show polyuria accompanied by hypermagnesuria [18], hyperphosphaturia, hypernatriuria, hyperkaluria and hypercalciuria. Serum electrolytes reflect the excess excretion observed in urine. Blood and urine osmolarity is normal. The predominant acid-base balance disorder reported is a metabolic alkalosis. Acid-base and electrolyte disorders in urine and blood begin to appear in CKD stage 2.

Renal ultrasound shows increased echogenicity, decreased corticomedullary ratio and irregular margins at advanced stages of CKD. Renal Doppler indicates normal blood flow in renal vasculature and parenchyma. Urinary tract and bladder ultrasound does not show malignant lesions. Ultrasound of the prostate shows normal echogenicity with no malignant lesions. Blood pressure is either normal or mildly elevated. ECG is normal in almost all the patients.

CINAC patients in El Salvador have few abnormalities of the carotid and aorto-iliac arteries but have significant tibial artery abnormalities [17]. Atherosclerosis in all upper arteries was rare, becoming more evident in the lower body and peaking in tibial arteries. One hypothesis for this selective damage could be their greater exposure to occupational toxic substances. Farmers’ legs, sometimes bare, are the parts that are mostly exposed to the agrochemicals during spraying. In the same study, investigators have detected sensorineural hearing loss and osteotendinous reflex disorders. Both heavy metals and organic solvents are known to cause sensorineural hearing loss [19].

### PATHOGENESIS AND HISTOPATHOLOGY

The morphological pattern of CINAC is described as chronic tubulo-interstitial nephritis, in both Sri Lanka and El Salvador [20, 21]. The main findings are interstitial fibrosis and tubular atrophy with or without inflammatory monocyte infiltration. In addition, generalized sclerosis, increased glomerular size, collapse of some glomerular tufts and lesions of extra-glomerular blood vessels (such as intimal proliferation and thickening and vacuolization of the tunica media) are also observed.

In a retrospective study of 251 renal biopsies, histopathological features of the first four stages of CINAC in Sri Lanka are described [22]. The predominant feature of stage 1 disease was mild and moderate interstitial fibrosis, while most cases did not demonstrate any evidence of interstitial inflammation. Glomerular sclerosis was absent in 62.3% of the cases. Stage 2 disease had moderate interstitial fibrosis with or without mild interstitial inflammation. Stage 3 disease had moderate and severe interstitial fibrosis, moderate inflammation, tubular atrophy and some glomerulosclerosis.

More interstitial fibrosis and tubular atrophy and less glomerulo-megaly when compared with non-sugarcane agricultural workers or non-agricultural workers were observed in 46 sugarcane workers with CINAC in El Salvador [21]. Likewise, more severe tubular atrophy was seen among sugarcane workers than non-sugarcane agricultural workers, along with greater mononuclear inflammatory infiltration. Biopsy findings support the clinical observations that males and females are suffering from the same disease in both Sri Lanka and El Salvador [21, 22].

The electron microscopy (EM) in proximal tubule showed multilaminated ‘myeloid’ structures of different sizes, probably related to an intracellular transport mechanism and degradation of substances by lysosomes. The occurrence of ‘myeloid bodies’ by EM is interesting as chloroquine toxicity and other types of drugs may evoke similar lesions [23]. There were several malaria epidemics in CINAC endemic areas in both El Salvador and Sri Lanka during the 20th century. However, consumption of chloroquine in relation to CINAC has not been studied; hence, it is premature to include occurrence of ‘myeloid bodies’ in the definition of CINAC.

### AETIOLOGY

Although the aetiology of CINAC is unclear, it appears to be multifactorial. Two aetiological hypotheses emphasizing different primary triggers have been proposed: one related to repeated and prolonged exposure to potential toxins at work, in the drinking water and the environment of the agricultural communities, while the other is related to heat stress with repeated episodes of dehydration. Many unfavourable social determinants are strongly associated with the aforementioned harmful factors. It can lead to a devastating work environment, affecting the whole body and the kidney in particular.

A study in Sri Lanka described several risk factors for CINAC: being a farmer, using pesticides, drinking well water, a family history of renal dysfunction, having taken Ayurvedic...
treatment and past history of snake bite [24]. A study published in 2011 found age more than 60 years, being a farmer, family history of CKD and exposure to agrochemicals were significant risk factors for CINAC [16]; a clear association with analgesic use was not found. Another study indicates elevated dietary cadmium (Cd) as a possible causative factor for the disease [25]. They reported high Cd content in lotus rhizomes, rice and tobacco, and concluded that the provisional tolerable weekly intake of Cd was high. A comparative study of rice grains from 12 countries demonstrated that the Cd content of Sri Lankan rice is high and only Bangladesh rice had a higher content [26]. The WHO research group pointed out that the risk for CINAC was increased in individuals aged more than 39 years and those engaged in vegetable cultivation. Further, they showed pesticide residues above the reference levels in 31.6% of the urine samples of CINAC patients. The detection frequency of 2,4-D, 3,5,6-trichloropyridinol, p-nitrophenol, 1-naphthol, 2-naphthol, glyphosate and aminomethylphosphonic acid (AMPA) was 33, 70, 58, 100, 100, 65 and 28% respectively in urine of CINAC patients [10]. They have also shown that the mean concentration of Cd in urine was significantly higher in those with CINAC (1.039 µg/g) compared with controls in the endemic (0.646 µg/g) and non-endemic areas (0.345 µg/g). The WHO study group found a significant dose effect relationship between the urine Cd concentration and stage of the CKD.

A study published in 2014 shows that the CINAC epidemic among farmers in the dry zone of Sri Lanka is associated with

<table>
<thead>
<tr>
<th>Table 2. Comparison of CINAC in Sri Lanka and Central America</th>
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<tbody>
<tr>
<td><strong>Sri Lanka</strong></td>
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<tr>
<td>Primarily among</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
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<td>Glomerulonephritis</td>
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<td>Risk factors</td>
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<tr>
<td>Clinical features</td>
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<tr>
<td>Asymptomatic (early stages)</td>
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<tr>
<td>Loss of appetite</td>
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<tr>
<td>Lethargy</td>
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<td>Backache</td>
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<td>Insomnia</td>
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<td>Arthralgia</td>
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<td>Muscle ache</td>
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<tr>
<td>Cramps</td>
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<td>Dysuria</td>
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<td>Foamy urine</td>
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<tr>
<td>Neurological abnormalities</td>
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<td>Sensorineural hearing loss</td>
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<td>Tibial artery abnormalities</td>
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<td>Liver enzyme level</td>
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<td>Urinary findings</td>
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<tr>
<td>Hyperuricosuria</td>
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<td>Hypertension</td>
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<td>Hyperphosphaturia</td>
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<td>Hypercalciumia</td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>β2-microglobulin, NAG, NGAL</td>
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<tr>
<td>Blood</td>
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<tr>
<td>Hyperuricaemia</td>
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<tr>
<td>Hypoanaemia</td>
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<td>Hypokalaemia</td>
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<td>Imaging</td>
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<td>Histopathology</td>
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<tr>
<td>Tubulo-intestinal nephritis</td>
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<tr>
<td>Interstitial fibrosis</td>
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<tr>
<td>Tubular atrophy</td>
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<tr>
<td>Interstitial mononuclear cell infiltration</td>
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<tr>
<td>Glomerulic collapse</td>
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<tr>
<td>Fibrous intimal thickening and arteriolar hyalinosis</td>
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<tr>
<td>Immunofluorescence tests</td>
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</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drugs; NAG, N-acetyl-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.
drinking well water, drinking water from abandoned wells and
with spraying glyphosate in paddy fields [27]. This study hy-
thesized chronic synergistic nephrotoxicity due to herbi-
cides, heavy metals and high ionicity in the ground water,
being the primary triggers, considering in addition chronic re-
peated dehydration as an important modulator of chemical
nephrotoxicity [28]. Working for more than 6 h daily in the
field standing in the sun, drinking water only from wells, con-
sumption of less than 3 L of water per day, and having a history of
malaria are factors that lead to the development of CINAC
in a study performed in Medawachchiya, an endemic area in
Sri Lanka [29]. A study performed in Padaviya and Meda-
wachchiya showed that the majority of CINAC-affected vil-

lages are located downstream, far away from the reservoirs
and irrigation canals [30]. In a cascade irrigation system agro-
chemical washout tends to accumulate downstream [31]. A
low prevalence of CINAC (1.5%) is noticed among consumers
of spring water, and high prevalence (7.7%) was identified
among consumers of water from shallow wells in Kebitigolla-
wara, a CINAC endemic area in Sri Lanka [9] (26). Springs wells
are originate from quartzite formation, are active throughout
the year and water flows continuously. Possibility of contam-
ination of these wells from agrochemicals is low as water is
coming from deep in the earth. However, water in shallow
wells is stagnant and maintains a close relationship with the
canal water. Low prevalence of CINAC among spring water
drinkers in the endemic region of CINAC strongly favours
entry of toxins via contaminated drinking water as a crucial
pathway.

Certain compounds present in ground water and soil in the
disease endemic area have been postulated as possible aetio-
logical factors for CINAC. A study done in 2011 hypothesized
that elevated levels of fluoride in ground water in certain areas
in Sri Lanka could be associated with increasing prevalence of
CINAC [32]. A recent study revealed that the numbers of
CINAC patients are high where concentrations of soil van-
adium are also high [33]. Ocharatoxin A, a naturally occurring
fungal toxin, was also speculated to be an aetiological agent for
CINAC in Sri Lanka. A study showed that it is a natural contam-
iant of cereals and pulses cultivated in CINAC endemic areas
but the levels detected were below the toxic limits [34]. Cyano-
bacterial toxin was also identified as a potential nephrotoxin in
the CINAC endemic areas [35]. However, contamination of
ground water in shallow wells and tube wells by cyanobacterial
toxin has not been reported. Further, there are no reports that
CINAC is associated with urothelial malignancies as seen in
Balkan endemic nephropathy (renamed aristolochic acid ne-
phropathy); hence, aristolochic acid contamination of foods is
an unlikely suspect.

Genetic susceptibility was identified as a risk factor for
CINAC by using a genome-wide association study (GWAS)
[36]. The GWAS yielded a genome-wide significant association
with CINAC for a single nucleotide polymorphism (SNP; rs6066043; P = 5.23 × 10 in quantitative trait locus analysis; P = 3.73 × 10 in dichotomous analysis) in SLC13A3 (sodium-
dependent dicarboxylate transporter member 3). For this
SNP, a population attributable fraction was 50% and odds
ratio was 2.13.

A study group working on Mesoamerican nephropathy has
shown recurrent dehydration (RD) has a role in the pathogen-
esis of CINAC [37]. Suggested pathophysio logic mechanisms
include sub-clinical rhabdomyolysis, effects of hyperuricaemia
and hyperuricosuria, hyperosmolarity-induced activation of
the aldose reductase-fructokinase pathway in the kidney, and
vasopressin effects [38–40]. Roncal-Jimenez and others [41]
pointed out that RD might cause renal injury by activation of
the polyl pathway, resulting in the generation of endogenous
fructose in the kidney that might subsequently induce renal in-
jury via metabolism by fructokinase. Fructose is not nephro-
toxic itself. However, after metabolized by fructokinase, it
results in uric acid, nephrotoxic oxidants and inflammatory
mediators. The proximal tubule is one of the major sites
where fructokinase is expressed. RD results in repeated stimu-
lation of aldose reductase with the generation of fructose in the
proximal tubule, leading to tubular injury and inflammation.
In certain instances fructose-containing beverages are used as a re-
hydration fluid by agricultural labourers. However, this should
be more carefully registered in future epidemiological studies.
In a recent animal experiment, pathology consistent with
that of CINAC, including elevated serum creatinine, proximal tubu-
lar injury, renal inflammation and fibrosis, was observed fol-
lowing repeated exposure to heat-stress-induced dehydration.
Interestingly, this pathology was not observed in fructokinase-defi-
cient mice. In addition it was shown in an animal study that
access to sufficient water during the dehydration period could
protect the kidney [41].

**IS HEAT STRESS AND DEHYDRATION
THE MAIN TRIGGER OF CINAC?**

A number of solid arguments question the major role of heat
stress and dehydration in the context of CINAC. The epidemic
scale growth of CINAC occurred in the 1990s in Sri Lanka and
Central America [3, 4] and is related to the rapid increase in the
usage of agrochemicals. Sudden change in the working condi-
tions, temperature or rainfall, however, was not observed
(Table 3). In Sri Lanka, the contemporary changes in agricul-
tural practices were in favour of reducing the physical activity
and risk of dehydration. In paddy farming, preparation of the
land is a labour-intensive activity that used cattle and buffaloes
for centuries. The major change occurred with the introduction
of a two-wheel mini-tractor in the late 1980s and early 1990s.
Almost concurrently, herbicides were applied on a large scale.
Sri Lankan paddy fields are not homogenous, and are located
closer to villages with big trees providing shade and shelter.

The dehydration hypothesis cannot explain the mosaic pat-
tern of geographical distribution of CINAC in Sri Lanka. Some
adjacent villages to CINAC-prevalent areas do not have the dis-
ease. No epidemic of CINAC is observed in the northern part
of Sri Lanka, where environmental conditions are harsher than
the endemic areas in adjacent NCP. It is important to note
that agrochemicals were sparsely used in the Northern Province
of Sri Lanka. The government prohibited the use of these agro-
chemicals during the conflict from 1980 to 2009 in view of the
potential of these agrochemicals being used in the production
of improvised explosive devices by terrorists. Similarly, CINAC epidemics or even isolated outbreaks are not reported from Cuba and Brazil, other sugarcane-cultivating countries having similar geo-climatic factors to the Central American region. Cuba has 51 nephrology departments around the country. All of them report monthly to the National Coordinator Centre case by case where the information is processed and controlled [42]. CINAC-compatible cases have not been reported to this registry from any department. R.H. (third author) has been working for 30 years in an outpatient renal clinic in Cuba and has never seen a single CINAC patient. Further, CINAC is not reported from Myanmar, a rice-cultivating Asian country that shares similar geo-climatic factors to Sri Lanka. Myanmar farmers have not been using agrochemicals abundantly due to the economic sanctions imposed.

In Sri Lanka and El Salvador a number of studies show a chronic interstitial nephritis in woman comparable to almost all aspects of the disease observed in male agricultural workers. These women are less or almost not at all exposed to the harsh working conditions, but developed CINAC [43]. This clinical condition in woman can only be explained by non-occupational exposure to the same toxins through ingestion or inhalation since they share the same environment as their male partners working in the sugarcane industry. There are a considerable number of construction workers in Colombo, Sri Lanka and the suburbs where agriculture practices are minimal. They are exposed to more heat during daytime compared with paddy farmers in the plains these symptoms. In addition, dehydration stimulates thirst with sugary drinks and sugarcane juice. However, the intake of contaminated water and aggravates the effects of the toxins, by increasing their concentration in the renal tubules, particularly those who undertake long work shifts, without adequate breaks and proper rehydration. In Central America the sugarcane workers are known to quench their thirst with sugary drinks and sugarcane juice. However, the high prevalence of CKD in children and adolescents has been reported in a descriptive epidemiologic study in three agricultural regions with known high prevalence of CINAC in El Salvador [44]. This suggests the possibility of early kidney damage prior to future occupational exposure to heat stress, dehydration or agrochemicals. Therefore, nephro-toxins in drinking water or food, maternal malnutrition, genetic susceptibility or any other exposures that might be present since childhood could be aetiological factors.

All over the world there are many individuals, e.g. those working in blast furnaces, miners working deep under the ground, who are exposed to the same harsh conditions as sugarcane workers and who have never developed rapidly progressive CIN. In miners who are submitted to regular health screening programmes in Belgium, France, the UK and many other countries, including for markers of renal damage, CINAC-like diseases have never been observed.

Some patients with CINAC show neurological symptoms such as sensorineural deafness, myoclonus and positive Babinski. Doppler ultrasound shows abnormalities in tibial arteries. These extra renal manifestations are not associated with ‘dehydration per se’. Toxic aetiology of the disease most likely explains these symptoms. In addition, dehydration stimulates the intake of contaminated water and aggravates the effects of the toxins, by increasing their concentration in the renal tubules, particularly those who undertake long work shifts, without adequate breaks and proper rehydration. In Central America the sugarcane workers are known to quench their thirst with sugary drinks and sugarcane juice. However, the

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sri Lanka</th>
<th>Central America (El Salvador)</th>
</tr>
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<tbody>
<tr>
<td>Crop</td>
<td>Rice main season (maha)</td>
<td>Sugar cane, maize</td>
</tr>
<tr>
<td>Land belongs to</td>
<td>Farmers</td>
<td>Beans, sorghum</td>
</tr>
<tr>
<td>Number of days work in the field per annum</td>
<td>30–40 days mainly males</td>
<td>6 months winter cereals</td>
</tr>
<tr>
<td>Average working hours per year Contribution by females</td>
<td>150–200 h</td>
<td>6 months summer sugarcane</td>
</tr>
<tr>
<td>Average temperature 8 am</td>
<td>27°C</td>
<td>27°C (coast)</td>
</tr>
<tr>
<td>Average temperature 12 pm</td>
<td>31°C</td>
<td>33°C</td>
</tr>
<tr>
<td>Average temperature 6 pm</td>
<td>27°C</td>
<td>28°C</td>
</tr>
<tr>
<td>Relative humidity</td>
<td>min 60%—July, max 80%—December</td>
<td>min 45%—March, max 74%—September</td>
</tr>
<tr>
<td>Annual rain fall in endemic region</td>
<td>1250–2000 mm</td>
<td>1900–2000 mm</td>
</tr>
<tr>
<td>CINAC first noticed in</td>
<td>1994</td>
<td>1999</td>
</tr>
<tr>
<td>Main fertilizers used in the region</td>
<td>Urea, potassium chloride, triple super phosphate</td>
<td>Ammonia sulphate and sugarcane formulae, triple super phosphate, urea</td>
</tr>
<tr>
<td>Main herbicide used in the region</td>
<td>Paraquat (1980s), glyphosate (1990s and after)</td>
<td>Paraquat, 2,4-D, glyphosate, triazines</td>
</tr>
<tr>
<td>Main insecticide used in the region</td>
<td>Chlorpyrifos (organophosphate)</td>
<td>Methyl parathion, methamidophos (organophosphate)</td>
</tr>
<tr>
<td>Use of persistent organic pollutant pesticides (e.g. DDT)</td>
<td>Heavily used in anti-malaria campaign (1945–75)</td>
<td>Heavily used for cotton cultivation (1955–90)</td>
</tr>
<tr>
<td>Effect of mechanization</td>
<td>Manual workload reduced remarkably after introduction of machines</td>
<td>35% reduction of work load</td>
</tr>
<tr>
<td>Natural contaminants in ground water</td>
<td>Fluoride, high hardness</td>
<td>Arsenic, high hardness</td>
</tr>
</tbody>
</table>
CONCLUSION

The differences in the incidence of CKD among patients exposed to similar environmental conditions and risk factors further support that a single agent is unlikely to be responsible for CINAC. It is more likely that a complex interaction among the proposed risk factors contributes to the eventual development of the disease. To that cascade of events are added other factors such as social determinants that make them particularly vulnerable to prior kidney damage, such as low birth weight, malaria, diabetes, hypertension, obesity, smoking, excessive alcohol consumption, and use of non-steroidal anti-inflammatory drugs and nephrotoxic medicinal plants [45].

The occupational and environmental toxins present in poverty-stricken agricultural communities in both regions present a basal risk to men, women and children who live in that environment. These toxins enter their bodies through contaminated water, food and inhalation. For males there is added exposure through spraying of pesticides without protective equipment, by inhalation and dermal absorption not only during spraying but also by working with contaminated soil and crops. That may explain why males have such a high prevalence of CINAC, and high CKD mortality rates. These observations point towards a dose–response pattern comparable to the case of aristolochic acid nephropathies [46]. Defining the disease as heat stress nephropathy without having adequate evidence, and underestimating the role of pesticides and heavy metals in this epidemic, could seriously undermine efforts to develop effective and urgently needed public health interventions for CINAC.

CONFLICT OF INTEREST STATEMENT

None declared.

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