Cadmium, the real link to chronic kidney disease causation in hotspots of rural Pondicherry and coastal Cuddalore areas!

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Chronic kidney disease (CKD) is rightly called as the silent killer; a major killer disease which accounts for being the 18th leading cause of death in the world population.[1] Prevalence of CKD is estimated to be 8–16% worldwide. 9 out of 10 people who have stage 3 CKD (moderately decreased kidney function) do not know it.[2-4] Worldwide, diabetes mellitus is the most common cause of CKD.[5] High blood pressure is the second leading cause of kidney failure in the US.[2,6]

Glomerulonephritis and unknown causes of CKD are more common in countries of Asia and sub-Saharan Africa.[7] Besides diabetes mellitus, hypertension, old age, and polypharmacy; other unknown intriguing causes are topped by entities such as chronic interstitial nephritis triggered by a whole gamut of environmental toxins and modern food additives. The incidence of renal failure increases with age and is three- to five-fold higher in ethnic minority populations. The poorest populations are at the highest risk.[7] In India, North Africa and several Middle Eastern countries, environmental pollution, toxins, pesticides, other chemicals, analgesic abuse, herbal medicines, and unregulated food additives have been attributed as causes of CKD.[7-10] Kai-Uwe eckardt and colleagues reported on the global burden of kidney disease affects more than 10% of the world's population, a similar burden to diabetes.[11]

Clusters of the cases of CKD of unknown origin have been reported in some areas of Sri Lanka and India.[12] Contamination of water, food, or both, by heavy metals, industrial chemicals, fertilizers, and pesticides has been suspected.[13] The unknown causes of CKD in most nephrology registries worldwide should raise alarm bells as its prevalence is either greater or comparable to other traditional causes for CKD.

In 2001, the average annual cost of the maintenance of CKD therapy was between the US $70 and $75 billion worldwide excluding kidney transplantation, and the predicted number of CKD patients will reach over 2 million in 2010.[3,4,14,16] The enormous costs of treatment lead to a large burden for the health-care systems, particularly in developing countries.

As there are well-preserved people with elevated renal parameters and in those without any obvious etiology, the question arising is whether it is worthwhile to speculate if this entity is some form of interstitial nephritis caused by some environmental contaminant, food additives, or habits that *per se* are contributory or causative factors and accelerated by other coincidental diseases or comorbidities. In the order of implication, we readily think of contaminants in (1) water, (2) sand/soil, (3) beverages and beer/alcoholic drinks, and (4) food common staple diet of the coastal areas being fishes.

A possible ubiquitous element is cadmium, present in water, food, meat, fish, soil/sand, and beer (alcoholic drinks).[16] Many patients present with the late-presenting chronic interstitial nephritis, are well preserved and have smallish kidneys and have evidence of predominantly tubulointerstitial, non-glomerular damage. This presentation is well noted in the Indo-Asian population, and it will be of great value to note its incidence in this part of India. Lead, chromium, arsenic, and mercury are the other commonly implicated heavy metals, but no associated features of their renal toxicity are commonly known.

Chronic toxic injury and depletion of intrinsic protective mechanisms result in chronic interstitial nephritis in the long run.[17] Cadmium accumulates in renal tubular cells bound to metallothionein, a small protein containing 30% cysteine.

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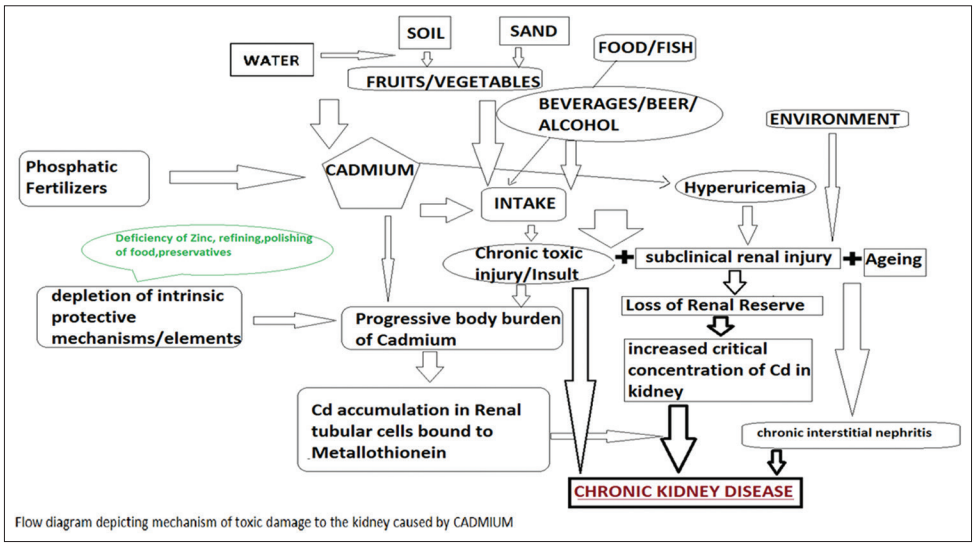

Figure 1: Mechanism of toxic damage to the kidney caused by cadmium

Metallothionein protects against nephrotoxicity by binding to cadmium in a nontoxic form. Chronic interstitial damage occurs when the critical concentration of cadmium in the renal cortex exceeds about 200 mg ms/g.[18] Most of the cadmium applied through phosphate fertilizers (especially in India) in sandy soils tend to stay in mobile forms (soluble or exchangeable). Hence, the risk of it leaching to underground water or its uptake by plants is higher.[19] Water pollution with cadmium causes Fanconi syndrome, osteomalacia, and chronic interstitial nephritis especially in old women, who were living near the riverside: Itai-itai disease.[20] An itai-itai model can be made in rats by long-term IV injection of cadmium chloride.[20] Exposure to occupational or relatively low environmental levels of cadmium appears to be a determinant for the development of end-stage renal disease.[21]

What if all the three, diabetes mellitus, hypertension, and CKD are caused by a single environmental toxin? More importantly, there is such a hotspot locality existing in coastal areas of Cuddalore in South India. There is a presence of heavy metal, cadmium in the water and obviously in the soil/sandy areas of the coastal town of Cuddalore, adjoining Pondicherry. The sipcot area community environmental monitors analysis from State Industries Promotion Corporation of Tamil Nadu (SIPCOT) area found that samples from four locations, including overhead tanks that cater to drinking water needs, contained high levels of carcinogens such as cadmium and chromium and other toxic heavy metals such as lead and iron. The levels of cadmium in samples collected from SIPCOT project office and other locations show a frightening concentration of 3–130 times above permissible limits.[22]

Common sources of cadmium are cigarettes and marijuana, refined foods (white flour, white sugar, etc.), tap water, some cold drinks, margarine, canned fruits and beverages, petrochemical pollution, nickel cadmium batteries, and fish and shellfish. There is the presence of cadmium in the industrial wastes, and many such industries exist in Cuddalore and Pondicherry. Cadmium levels are noted in wine, beer, and other alcoholic beverages, as these beverages are widely consumed, they contribute a large fraction of cadmium intake, and strict control of this element is advisable.[23]

There is a high level of the consumption of alcohol as the tax levied on these drinks is low in these localities. There is a high probability of the serum uric acid being high in these alcohol consumers. Cadmium is known to concentrate heavily in the presence of uric acid. Cadmium concentrates in the presence of hyperuricemia. The Land horse concentrates cadmium to the level of 200 mg/kg body weight in the renal cortex. In mammals and birds, cadmium accumulates at a concentration of 0.1–2 mg/kg and 1–10 mg/kg net wt. Kidneys in penguins show 5–160 mg/kg of cadmium: All exhibit chronic interstitial nephritis.[24]

The soil in coastal areas is sandy and porous. The level of groundwater has been steadily decreasing. There is a saline intrusion from the sea. All these factors cause increased cadmium intake which deposits in the kidneys and eventually cause CKD Figure 1. We can draw a parallel here with the balkan nephropathy,[25] itai-itai disease in Japan,[20] and the battery factories in Sweden.[21]

Cadmium has the potential to destroy the beta cells in the pancreas and cause diabetes mellitus. Recent epidemiological studies suggest a positive association between exposure to the environmental pollutant cadmium and the incidence and severity of diabetes. Findings indicate that cadmium may be a factor in the development of some types of diabetes and they raise the possibility that cadmium and diabetes-related hyperglycemia may act synergistically to damage the kidney.[26]

Cadmium also causes the development of hypertension. The conclusions are that one common form of hypertension is

probably an example of the accumulation of cadmium in the kidney.[27]

Adverse effects of cadmium on kidney and bone have been observed in environmentally exposed populations at frequencies higher than those predicted from models of exposure.[28] One study supports the hypothesis that environmental exposure to cadmium may increase the risk of hypertension.[29] Some findings add to the concern of renal and cardiovascular cadmium toxicity at chronic low levels of exposure in the general population.[30]

This part of rural India cannot afford dialysis as most of the local population is poor. Hence, it is of utmost urgency that the population be screened on a war footing for the presence of cadmium nephropathy and CKD and educate the people.

It is important that we revert to "our past ancestors habits in the caveman days" by modifying our present day lifestyle with the use of umpteen preservatives in all our foods. Our modern lifestyle has a penchant for artificial, attractive packaged foods with loss of all the protective elements such as zinc in them caused by the various processes of refining, cutting, and polishing. This allows the heavy metal to attack the organs with impunity as there are no protective elements to challenge them. Early detection and education can help prevent the progression of kidney disease to kidney failure.[1,6,15,31-35] Late detection is the lost opportunity for making any lifestyle changes and treats the aggravating factors.[1,31,35]

Primary prevention of CKD may be initiated by first looking for risk factors/antecedent conditions in the population involved with age ≥50 years, hypertension, diabetes mellitus, and family history of CKD, to aim for better control of risk factors involved, promote better awareness of CKD, and educate the population involved at risk using comprehensive public health initiatives and strategies. Screening must be done for cadmium/heavy metals by spectrophotometric analysis in blood, urine of high-risk individuals and in the soil samples, fertilizers, fruits, and vegetables, fish, alcohol, and groundwater samples especially in the affected areas in Cuddalore/Pondicherry.

The government and the industries must be aware of their social obligations and to try to dispose of the industrial wastes away from water sources using better ingenious methods. Effective legislation needs to be put in place to check the deficiencies or errant behaviors by the concerned industries. Efforts should be directed to ban usage of cadmium in fertilizers and Nickel Cadmium batteries as done in Europe.

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