

Evaluation of the Etiology of Chronic Kidney Disease of Unknown Etiology Beyond Heat Stress, A systematic Review: A Pakistani Perspective

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Abstract:

Objective:

Chronic kidney disease of unknown origin (CKDu) is emerging as an important public health problem in Pakistan, where conventional risk factors like diabetes and hypertension do not fully explain its rising prevalence. This review aims to analyze the multifactorial etiology of CKDu in the Pakistani context, stressing upon environmental and occupational exposures beyond the widely discussed heat stress hypothesis.

Methodology:

The PRISMA 2020 guidelines were followed. Studies were selected according to the PECO model to assess the relation of environmental pollution with CKD. Search was done through PubMed, Google Scholar, Pakmedinet, and Euromed. We included only English literature articles emphasizing the volume of these pollutants in Pakistan.

Results:

This review shows that there is a significant impact of changing environmental dynamics on Pakistan, which is causing profound adverse effects on the quality of water, air, and food. This change is affecting the epidemiology and demography of various diseases, along with CKDu. About 120 articles were selected, out of which 48 were included in the review due to relevance to the topic.

Conclusion:

The recent recognition of microplastic, nanoplastic dust particles, heavy metals, premature birth, or low birth weight might be a cause of CKD in patients who do not live in agricultural areas. There is a need to look at the etiology at the community level, as it seems that early intervention can prevent this important cause of CKD.

Keywords:

Chronic kidney disease, CKDu, Environmental toxins, Arsenic, Ochratoxin, Pakistan

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Introduction

Pathophysiological and Epidemiological Overview of CKDu

Approximately 850 million people around the globe are estimated to have kidney disease (1). This rising prevalence is asymmetrically high in low-income countries (LIC) and lower-middle-income countries (LMIC) (2). Multiple factors contribute to the exponentially high prevalence of chronic kidney disease (CKD) in these regions. These factors included firstly the environmental changes

like global warming, air and water pollution, secondly, the increasing prevalence of infectious diseases like malaria and dengue, and lastly, non-infectious AKI like Snake bite, pregnancy-related AKI (3).

A recent worldwide study of 12 LMICs has reported a CKD prevalence of 14.3% in the general population and 36.1% in high-risk groups (4). In Pakistan, Ashar and Farhana found an overall CKD prevalence of 16.6% in the community in the cosmopolitan city of Karachi (5). CKD in Pakistan, as elsewhere, is mostly caused by diabetes mellitus and hypertension, followed by kidney stones, glomerulonephritis, and chronic kidney disease of unknown etiology (CKDu). (6) The increasing prevalence of CKDu in Pakistan is concerning. Multiple studies have been done internationally to identify a particular offending agent in affected geographical areas to explore non-communicable disease (NCD) hotspots. (7). Since there is no population-based study in Pakistan, exploring the relation of these factors to CKD incidence in Pakistan is needed. The reported incidence and prevalence of CKDu in hospital-based studies are 9.1% and 26.1%, respectively. (8,9).

Methodology:

The PRISMA 2020 guidelines were followed. Studies were selected according to the PECO model to assess the relation of environmental pollution with CKD. Search was done through PubMed, Google Scholar, Pakmedinet, and Euromed. We included only English literature articles emphasizing the volume of these pollutants in Pakistan. About 120 articles were selected, out of which 48 were included in the review due to relevance to the topic.

Since it is a systematic review no IRB approval was required.

Environmental and Occupational Exposures

1) Heat exposure (dehydration vs rehydration):

In recent years, an increasing number of inhabitants of Central America, Sri Lanka, India, and other temperate areas have developed a form of chronic kidney disease, now recognized as CKDu. This disease characteristically occurs in young male agricultural workers exposed to very hot conditions. The majority of them present with normal or mildly elevated blood pressure, reduction in estimated glomerular filtration rate (eGFR), non-nephrotic proteinuria, hyperuricemia, and hypokalemia (10). The exact cause of the disease is not yet established, although one group of investigators proposed that dehydration along with heat stress, rhabdomyolysis, and hyperuricemia are likely factors leading to this epidemic. They suggested that recurrent dehydration may induce renal injury via a fructokinase-dependent mechanism, likely from the generation of endogenous fructose and the polyol pathway. They postulated that the epidemic of CKDu may be a consequence of global warming, leading to excessive dehydration (11).

On the contrary, another group proposed that persons working in agricultural fields are exposed to very hot and humid climatic conditions. As a consequence, they perspire abundantly and they drink more fluids. Sugarcane farmers, while working in the fields, may drink nearly 8 – 12 L of water/day. In this environment, even if contaminants of the drinking water do not reach what are ordinarily considered 'toxic concentrations, given the enormous amount of fluid intake, workers may end up ingesting a daily extensive quantity of environmental toxins such as heavy metals, pesticides, arsenic, or other agents (12). Since the disease is prevalent in hot tropical countries, this augmented

a belief in the hypothesis of heat stress and dehydration as a cause of CKD. This was the reason that some authors called it global warming nephropathy and described CKDu as an epidemic caused by the effects of global warming (13).

On the contrary, in a cross-sectional study done in Sri Lanka, on three occupational groups according to the climate regions. (In Sri Lanka, there are three agro-climatic zones: wet, intermediate, and dry zones with distinct climates). The study revealed that heat exposure alone does not appear to be the leading and only cause of CKDu., This is more likely to be associated with other risk factors such as pesticides, nanoplastics, microparticles, and other chemical exposures (14). This finding extended the cause of CKDu to look into the other factors. In Pakistan, there is a need to evaluate these factors and their impact on the rising CKD burden.

2) Arsenic:

Industrial toxins, particularly heavy metals such as arsenic, cadmium, copper sulfate, lead, and various mycotoxins like zearalenone and ochratoxin, are associated with renal and genitourinary diseases (13,14,15,16). Since Arsenic is the most abundant contaminant, we will discuss it in detail.

The Pakistan Council of Research in Water Resources evaluates arsenic levels regularly in the major cities of Pakistan. (17) Persistently increasing arsenic contamination led to a national action plan initiated in 2007. A nationwide survey of drinking water was evaluated in 35 of 104 districts. Of 8712 samples, only 9% had arsenic levels meeting the WHO standard of 10 Parts per billion (ppb). Almost 30% had levels above 10 ppb when validated by atomic absorption spectrometry, and 77% had levels above 50 ppb. The highest values were seen in the Sindh province (18).

Analysis of drinking water from Sheikhpura and Multan District in Punjab. High levels of arsenic were found in hand pump samples (76.22 ± 20.73 ppb) and were only just acceptably lower in bottled water here (7.742 ± 3.066 ppb) (19,20). Studies from Sindh have reported alarming arsenic levels, with groundwater measuring $96 \mu\text{g/L}$ and surface water reaching up to $157 \mu\text{g/L}$, far exceeding the WHO safety threshold, which is $10 \mu\text{g/L}$ (21,22).

In Manchar Lake, the largest reservoir of fresh water in Pakistan, the levels were in the range of $35.2\text{--}158 \mu\text{g/L}$, surpassing the limit by 3-15-fold. In Jamshoro, Sindh, the highest content of arsenic in surface water samples was found to be $50 \mu\text{g/L}$ (23). Consumption of food with higher levels of arsenic can cause kidney failure. There is evidence of the effects of arsenic on the renal system of humans by consuming 20 ounces of chicken 5 times a week, showing the toxic levels of urinary arsenic ($126 \mu\text{gms}$ vs $50 \mu\text{gms}$ normal) and renal failure (24).

Arsenic occurs naturally in both organic and inorganic forms. Organic arsenic compounds have been used in the poultry industry for years. Roxarsone (Ristar; 3-nitro, 4-hydroxy-3-nitrobenzenearsonic acid) is an arsenic-containing component of chicken feed that performs multiple functions, like it nurtures chicks' growth, ameliorating the efficiency of feed utilization, and enhancing meat pigmentation. It also controls the dissemination of coccidiosis, a protozoan disease that is the sole destroyer of farmed chickens (25). However, over 90% of arsenic is excreted unchanged in the feces. Unprocessed human waste containing arsenic, which is largely excreted unchanged, can contaminate soil when used as fertilizer, leading to arsenic accumulation in crops like maize, wheat, and rice, thus posing a health risk. (26)

Soil bacteria, particularly *Clostridium* species, transform organic arsenic into various forms, including dimethyl arsenic acid, monomethyl arsenic acid, and inorganic arsenic compounds. These metabolites are more toxic than the original precursors found in the environment (27,28). Uncovered chicken litter storage leads to environmental contamination as rainfall causes arsenic to leach and contaminate nearby water sources like rivers, streams, and wells (29). Meliker et al investigated the relationship between moderate arsenic levels and selected disease outcomes and found a significant association between arsenic exposure and CKD (30).

3) Ochratoxin A:

Ochratoxins, another class of mycotoxins, are produced by *Aspergillus* and *Penicillium* species. Of the three forms, A, B, and C, ochratoxin A (OTA) is the most toxic. It is a powerful nephrotoxin, carcinogen, teratogen, and immunotoxin (31).

Poultry is recognized as a major food source contaminated with ochratoxin (32). In a Pakistani study by Fareed et al, the OTA levels in poultry feed were evaluated, and ochratoxin contamination was detected in 63% of poultry feed ingredients and 29% of finished feed products. (33). Abid et al investigated OTA levels in mixed poultry feed and its ingredients collected from farms and markets in Lahore, Pakistan. They collected the samples across three-time intervals: during the hot and humid climate, i.e., July to October, in winter, November to February, and in a moderate climate, i.e., from March to June. The incidence of OTA-positive samples was highest from July to October (82%), followed by March to June (67%), and lowest from November to February (58%). The study concluded that the widespread contamination of poultry feed ingredients like canola, soybean, sunflower meal, maize, and whole cotton seeds (mycotoxin), with OTA represents a serious and irreversible public health concern requiring urgent intervention. (34).

4) Microplastic:

Microplastics (MP) and nanoplastics are a global concern now because they are widely distributed in soil, freshwater, seawater, and the atmosphere, and they have also been found in seafood, sea salt, and various foods, and have a negative biological effect. Both microplastics and nanoplastics are small synthetic organic polymer particles of < 5mm and <1 μ m, respectively (35). There is evidence of the presence of microplastics in the Placenta, lungs, liver, blood, heart, and human body fluids. These particles can enter the body from any route, such as the gastrointestinal, pulmonary, and even skin contact, and have the potential to alter the body's metabolism. They can promote inflammation, oxidative stress, and precipitate dysfunction of body organs at the cellular level (36).

In a well-developed animal model, Xiong and Goa treated mice with different diameters of Microplastic (80 nm, 0.5 μ m, 5 μ m). The histological analysis, which was done at the 8th week of exposure, showed that there is mesangial matrix expansion, endocapillary proliferation, tubulointerstitial fibrosis, and inflammatory infiltration in mice' kidneys. Further analysis at the molecular level revealed increased levels of malonaldehyde and inflammatory markers IL-1 β and MCP-1. Tubulointerstitial fibrosis was demonstrated by the Trichrome Masson stain showed high-collagen deposition and higher Alpha Smooth Muscles Actin (α SMA) expression after exposure to MPs, when analyzing molecular levels. They also compared the serum creatinine levels in animals that were exposed to the 5 μ m MPs group to the control group. To explore the mechanisms that lead to kidney fibrosis in the MPs' exposed group, they performed transcriptome analysis. With the use

of Gene Ontology enrichment Analysis, chronic exposure resulted in enrichment in immune-related signals and is significant with circadian rhythm (37).

There are important questions that need to be answered in patients with CKD and patients on hemodialysis, like a decrease in kidney function promotes more accumulation of MPs in CKD patients. Kidney replacement therapies, both hemodialysis and peritoneal dialysis, are unthinkable without plastics, the peritoneal dialysis bags, tubing, dialyzers, the stuff of RO water, etc, all plastics. There is a need to explore whether these MPs are dialyzable or further deposits of MPs in ESRD patients on any of the therapies.

In Pakistan alone, 3.3 million tons of plastic waste are generated annually, equivalent to the height of two K2 Mountains. Pakistan alone generated about 3.9 billion kilograms of plastic waste in 2020, with 70% of it ending up in landfills or improperly disposed of into the environment, exacerbating soil and water pollution. (38).

5) Air Particles:

Air pollution is defined as the alteration of the internal as well as external environment by any chemical, physical, or biological agent that changes the natural quality of that territory or habitat. It comprises a complex mixture of particulate matter (PM) and gaseous pollutants. PM can be categorized into PM₁₀ and PM_{2.5}. Their association with cardiovascular and respiratory system diseases is well established; recent research suggests that air pollution also has a significant, yet underappreciated, impact on kidney health (39).

In a nationwide study conducted in China, the investigators reported that exposure to SO₂ carried the highest risk of kidney disease. They calculated that each 10 μ g/m³ increment in the lag 0-1 mean concentration of SO₂ was associated with a 2.9% increase in death from kidney disease, followed by NO₂ and PM (40). Similarly, Studies by Lee et al and Wu et al have linked air pollution to hospitalizations and increased emergency department turnover due to kidney disorders, particularly with O₃, CO, and SO₂ associated with acute kidney injury and CKD (41,42). In like manner, Bi et al found that the PM_{2.5} component mostly includes elemental carbon and organic carbon, and O₃ was associated with increased emergency department visits for kidney diseases in Atlanta and Georgia (43). Chin et al, in a fascinating case-control study, showed that people residing near a petrochemical industrial park had a higher risk of chronic glomerular disease (44).

In 2019, Pakistan came in with a PM_{2.5} reading of 65.81 μ g/m³, not only putting it into the 'unhealthy' ratings category, which requires a reading of anywhere between 55.5 to 150.4 μ g/m³ to be classed as such, but also into the 2nd place position out of the most polluted countries in the world. Two of its major cities, Gujranwala and Faisalabad, both came in the top 5 most polluted cities, taking 3rd and 4th place, with PM_{2.5} readings of 105.3 μ g/m³ and 104.6 μ g/m³, respectively, numbers that place them in the higher end of the unhealthy bracket (45)

In Pakistan, PM is a major air pollutant, causing serious health problems. In an analysis, Asghar and Ali et al measured the concentration of PM in ambient air and its associated health risk in Haripur city in the northern area of Pakistan. Twenty-three sites were selected at various educational institutes, hospitals, recreational areas, and industries in the city, and air samples were taken at each site. The concentration of PM_{2.5} μ g/m³ and PM₁₀ μ g/m³ was measured with the Youngteng YT-

HPC 3000A portable PM counter. The results revealed that the values of both PM_{2.5} and PM₁₀ were above the permissible limits of 35 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and 150 $\mu\text{g}/\text{m}^3$ for PM₁₀ set by the Environmental Protection Agency Pakistan (Pak-EPA) in all the educational institutions, hospitals, recreational areas, and industries investigated. In addition, there was a significant ($p<0.05$) variation in the concentrations of both PM_{2.5} and PM₁₀ in areas under study. The concentration of PM_{2.5} was positively correlated with the concentration of PM₁₀ in all the sampling sites. Therefore, from a 1-14 scale standard of health index, the values of PM_{2.5} and PM₁₀ exhibited that the ambient air quality of Haripur city, Pakistan, is at high risk (46).

Developmental And Biological Risk Factors (Low Birth Weight, Preterm Birth)

Human nephrogenesis is complete before birth at 34 to 36 weeks of gestation, with 60% of nephrons forming during the third trimester. Preterm birth is associated with low nephron endowment, with an increased risk of chronic kidney disease later in life. About 60% of nephrons are formed during the third trimester of pregnancy, and preterm birth or kidney damage during this period can impair nephrogenesis and reduce the number of nephrons, potentially leading to long-term kidney damage. To compensate for this loss, there is hyperfiltration in remaining of the remaining nephrons, and this persistent hyperfiltration for a longer period, according to Brenner's hypothesis, leads to hypertension, proteinuria, and kidney dysfunction (47).

In a Norwegian retrospective longitudinal cohort study, individuals with low birth weight (1100 – 2300 g) and individuals with normal birth weight (3500 – 4000 g) aged 41 – 52 years were evaluated. There was a significant difference in eGFR in women who were born with low birth weight as compared with normal birth weight women; interestingly, there was no such difference found in men (48).

In another recently done cohort of 277,252 participants free of CKD at baseline from the United Kingdom Biobank (UKB) prospective cohort, Dai and Zhuang reported that after a median follow-up of 11.9 years, they identified 13,030 (4.7%) CKD cases. Compared with normal birth weight (2.5 – 4.0 kg), low birth weight (LBW, <2.5 kg) was associated with an 11% higher risk of CKD in men (adjusted hazard ratio [HR]: 1.11 [95% CI 1.01 – 1.21]) and a 27% higher risk of CKD in women (HR: 1.27 [1.19 – 1.36]) (p for interaction = 0.02). High birth weight (HBW, >4.0 kg) was associated with an 11% lower risk of CKD (49).

In a data analysis of rural communities in six low- and middle-income countries namely, the Democratic Republic of the Congo, Zambia, Guatemala, India, Kenya, and Pakistan using the Global Network population-based registry of pregnant women and their babies. Pakistan has significantly high indices of both low birth weight and premature birth. The overall rate of preterm birth was 12.6%, with the lowest rate observed in Belagavi, India, 8.6%, and the highest in the Pakistani site, 21.8%. The overall LBW rate was 13.6%, with the lowest rate at the Kenyan site, 2.7%, and the highest at the Pakistani site, 21.4%. The overall rate of both preterm birth and LBW was 5.5%, with the lowest rate in the Kenyan site, 1.2%, and the highest in the Pakistani site, 11.0% (50). Similarly, studies in other parts of the country, such as in Muzaffarabad, Azad Kashmir, Sind, and Peshawar, have shown a significantly low birth weight and its impact on children's growth in their future life in Pakistan (51,52,53).

Diagnostic Confusion And Epidemiological Gaps

Hypertensive nephropathy and chronic glomerulonephritis.

The two important diagnostic criteria of hypertensive nephropathy are hypertension and CKD, while more than 80 % of CKD patients have hypertension. CKD patients with hypertension will fulfill diagnostic criteria for hypertensive nephropathy, especially when no diagnostic workup is done (54). There is a dubious, rather inverse relationship between the burden of hypertension and hypertensive nephropathy as a cause of renal replacement therapy in the USA and Europe (55,56). By definition, we are labelling CKDu as hypertensive nephropathy (57). This area also needs to be searched to know the exact relationship between hypertension leading to nephropathy vs nephropathy causing hypertension. In Pakistan, the mean age of the CKD population reported in different studies is 40 to 45 years, and hypertension is reported to cause CKD in nearly 16% of the patients in the majority of studies. Similarly, chronic glomerulonephritis is mostly a clinical diagnosis, and patients who present with hypertension and proteinuria without any history of pedal or periorbital edema, frothing of urine are also labeled as chronic glomerulonephritis (58). If both diseases are correctly labelled as CKDu, the incidence will increase further. All factors are summarized in **Table 1**.

Table 1: Summary of Environmental, Occupational, and Non-Traditional Risk Factors Associated with CKDu

Category	Specific Factor	Supporting Studies (Ref #)	Key Notes / Evidence Summary
Environmental Toxins	Arsenic in drinking water	17 – 30	Groundwater contamination in Pakistan and other LMICs is widely implicated in CKDu pathogenesis.
	Mycotoxins (Ochratoxin A, Aflatoxins)	31 – 34	Common in poultry feed; nephrotoxic effects under under-reported in Pakistan.
	Heavy metals (lead, cadmium, mercury)	15	Known nephrotoxins; detected in rural water supplies and industrial zones.
	Microplastics and plastic waste exposure	35 – 38	Emerging evidence of nephrotoxic effects; documented in animal models and polluted communities.
	Air pollution (PM _{2.5} , NO ₂ , SO ₂ , etc.)	39 – 46	Short-term and long-term exposure linked to hospital visits and kidney-related mortality.
Occupational Risks	Heat stress and dehydration	10 – 14	Key hypothesis in CKDu endemic areas (Sri Lanka, Central America); unclear in South Asian data.
	Farming & agrochemical handling	10, 14	Direct exposure without protective gear increases CKDu risk.
Food Chain Exposure	Poultry industry waste (e.g., Roxarson)	16, 25 – 29	Inorganic arsenic in chicken litter can contaminate soil and water.
Biological/ Perinatal	Low birth weight and nephron underdevelopment	47 – 53	Low nephron number increases CKD risk later in life.

Traditional CKD Risks	Hypertension	54, 55, 57	Often coexists or follows CKDu; difficult to separate as the primary cause.
	Diabetes	6, 56	Usually excluded in CKDu definitions, but may complicate diagnosis.

PM₂, Particulate Matter 2 microns. NO₂ Nitrogen dioxide. SO₂ Sulfur dioxide

Conclusions And Recommendations

CKDu is now a recognized cause of CKD. At the onset of its recognition as the cause of CKD, its etiology was debatable, and the arguments were both in favor of water deprivation or dehydration or excess of water intake with contamination with pesticides, heavy metals, etc., in agricultural communities. Over the last couple of years, it has been well recognized that it is not only heat stress or water deprivation, but rather it is multifactorial.

The recent recognition of microplastic, nanoplastic dust particles, heavy metals, premature birth, or low birth weight might be a cause in patients who are not living in agricultural areas. There is a need to look at the etiology at the community level, as it seems that early intervention can prevent this important cause of CKD. In this context, there is a need to:

- Conduct longitudinal community-based CKDu surveillance.
- Strengthen the regulation of groundwater and agricultural contaminants.
- Incorporate CKDu screening in rural health programs
- Promote environmental monitoring and public awareness

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