**PREVALENCE OF CHRONIC KIDNEY DISEASE OF UNKNOWN ETIOLOGY IN INDIA**

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**ABSTRACT**

The worldwide burden of CKD is critical and producing greater impact on health in the last 20 years. Lately, CKD of unknown origin ( CKDu), a kind of CKD seen in rural agricultural populations and there is no single standard cause of CKDu. CKDu was most generally linked with men, middle age, snake bite, illness, and exposure to agrochemicals, heavy metals, herbal drugs and heat stress across all geographical regions. Disease development can be successfully delayed by early identification, improved screening and care approaches are critical. In contrast to traditional biomarkers, the advanced biomarkers are with better sensitivity and specificity which are being proposed as potentially useful tools for illness early detection. Individual and community health awareness are immediately demanded for early screening of risk factors and timely intervention. It is also essential to develop health-care networks in order to enhance patient safety and quality of life. Also further etiological and interventional exploration is demanded to exclude avoidable indigenous risk factors and to develop visionary, all-encompassing methods for disease prevention and treatment.

**KEY WORDS**

Renal disease, heavy metals, agrochemicals, renal biomarkers, renal replacement therapy

**INTRODUCTION**

Chronic kidney disease is a condition characterized by structural and functional abnormalities of the kidneys induced by wide range of factors. Chronic kidney disease is also defined as a decline in kidney function, such as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1 73 m2, or other indicators of kidney damage, such as albuminuria, haematuria, or abnormalities discovered through laboratory testing or imaging that have been present for at least 3 months**.** (1). The significant causes of CKD are diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis, long-term use of anti-inflammatory medicines, autoimmune diseases, and polycystic kidney disease. (2). And the CKD which do not cause by these traditional factors are termed as CKD of unknown etiology. This is identified only in the later stages and also it has the tendency to progress rapidly, it has high chances of fatality (3). The worldwide burden of CKD has increased significantly during the last 20 years(4). Until 2008, the number of CKD-related deaths in India was at 5.2 million, and it is elevated to 7.63 million by 2020. (5). There are several environmental factors which are suspected to cause CKD of unknown etiology such as heavy metals, agrochemical use, mycotoxins and snake bite (6). As CKD of unknown etiology is becoming more widely recognized throughout India, specific systemic investigations and extensive epidemiologic research are needed to establish a definitive cause (7).

**PREVALENCE AND EPIDEMIOLOGY**

On a worldwide scale, end-stage renal disease (ESRD) and chronic kidney disease (CKD) are now serious public health challenges. These diseases increase patient morbidity and death (8). Until 2008, the number of CKD-related deaths in India was at 5.2 million, and it is elevated to 7.63 million by 2020. (5). The mean age of CKDu cases is 36.78 ± 9.85 years. Males (73.9%) were generally affected (9). The endemic population has an 8% incidence of CKD of unknown cause (10). The most prevalent cause for CKD is diabetic nephropathy (31%), followed by CKD of unknown origin (16%), chronic glomerulonephritis (14%), and hypertensive nephrosclerosis (13%). Patients presenting to public sector hospitals were poorer, younger, and had CKD of unknown origin more commonly (11).The majority of the patients having CKDu are manual workers engaged in outdoor activities (12). Long-term dehydration, analgesic misuse, hereditary factors, pesticide exposure, and heavy metal pollution of drinking water have all been linked to potential causes of CKDu (13).

**CLINICAL PRESENTATION AND DIAGNOSTIC CHALLENGES**

The pace of kidney function loss varies depending upon the etiology, exposures, and mostly subjective, but in most cases, progression to renal failure takes months to decades. Increased uraemia, anaemia, volume overload, electrolyte imbalances, mineral and bone disorders, and acidaemia induce kidney failure symptoms and mortality if left untreated(14). CKD is categorized into five stages according to GFR (15).

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|  STAGES | GFR Value ml/min/1.73 m2 |  CLASSIFICATION |
| I |  >90 | Normal or high |
| II | 60 – 89 | Slightly decreased |
| III A | 45 – 59 | Mild to moderately decreased |
| III B | 30 – 44 | Moderately to severely decreased |
| IV | 15 – 29 | Severely decreased |
| V | <15 | Kidney Failure |

Kidney Disease Improving Global Outcome (KDIGO) gives guidelines for assessing the CKD by analyzing the four main biomarkers such as creatinine, potassium, urea and albiminuria (16). Even with well-known biomarkers and risk factors, CKDu is often diagnosed only when the patient is in the last stages of the illness, requiring dialysis and kidney transplantation in the majority of circumstances (17). The various factors influencing the diagnostic limitations of CKDu prevention includes a lack of knowledge about the specific cause(s) of CKDu and limited access to early CKD diagnosis and care, including RRT; as well as a shortage of health care workers and trained personnel, a lack of funding, and a high prevalence of social determinants of ill health, among others (18).

**POTENTIAL CAUSES AND RISK FACTORS**

The heat stress/dehydration theory states that CKD is characterized by recurring mild acute renal injury caused by repeated work-related dehydration episodes. Dehydration increases osmolarity, which activates the aldose reductase enzyme in the proximal tubule of the nephron. This enzyme works in the polyol route of glucose metabolism, which converts glucose to fructose. Fructokinase metabolism results in oxidative stress, which damages tubules (19)**.**

Even though some heavy metals are helping in enhancing of normal physiological functions, if their limit exceeds they become dangerous to the same human body (20). Agrochemicals and fertilizers are heavily suspected to cause CKDu as they contain huge amount of heavy metals such as Cu, Cr, Cd, Cu, Ni, Zn, Mn, and Pb (21). Exposure to such metals in drinking water affects structural and functional integrity of kidneys results in renal tubular necrosis and glomerular collapse (22).

 Studies shows that elevation of Hantavirus IgG antibodies are also been the risk factor of developing CKDu with other known factors such as consumption of alcohol, tobacco chewing and cigarette smoking(23).

**INVESTIGATIVE APPROACHES**

 Kidneys carry out their most biological processes through tubule cells and allocate their vast energy for the process of electrolyte transport, acid-base homeostasis and endocrine functions. Kidney injury is not only restricted to glomerular functioning alone but it will results in tubular atropy and tubulointerstitial fibrosis which is commonly seen in all types of CKD (24). As serum creatinine is considered as the hallmark for measurement of kidney functions it have certain limitations as it is influenced by variety of factors such as muscle mass, diet and tubular secretion, also only through serum creatinine measurement, kidney injury cannot be differentiated between benign hemodynamic changes versus intrinsic kidney injury (25). Hence the introduction of biomarkers in assessing the kidney function greatly helps to determine the type and extend of kidney injury. The renal biomarkers are Kidney Injury Marker 1 (KIM-1), Epidermal Growth Factor (EGF), Monocyte Chemoattractant Protein 1 (MCP-1), α1 – microglobulin (AIM), hippurate or furosemide and uromodulin (26). Kidney tubule biomarkers will be crucial in building a global kidney health panel that can improve kidney disease diagnosis and management for persons at risk. (27).

 Saliva is a complex biological fluid and changes in its composition such as increase in salivary pH, buffer capacity, high levels of creatinine, potassium, chloride, salivary amylase can also be used as a diagnostic tool for CKD (28). Salivary inflammatory cytokines (TNF α, interleukin (IL) 1β, γ-interferon (γ-INF), IL-6, IL-8), IgA, IgB and IgC were also in high concentration in saliva of CKD patients (29). There are various advantages in using saliva as a diagnostic fluid. Also Saliva collection is quick, simple, low-cost, and non-invasive (30). These are the novel methods to be implemented for the earlier identification of kidney injury.

**PREVENTION AND PUBLIC HEALTH STRATEGIES**

 Political, cultural, economical, and health-care system-related variables, as well as a lack of coordinated research and inadequate financing, were recognized as important hurdles for the management of CKDU at India (31). Eventhough certain measures can be taken to improve public health.

1. The establishment of a multidisciplinary CKD Consortium to direct the national CKD research and response agenda - This group should include nephrologists, epidemiologists, and environmental scientists. Among those who have contributed to this effort are health professionals, basic scientists, social scientists, anthropologists, health economists, community groups, and patient advocates.
2. Guidelines for clinical and diagnostic assessment, as well as criteria for referral and management of CKD, should be developed and disseminated through professional associations and educational institutions at all levels of health care, including primary care, health centers, and district hospitals. The newly announced Standard Treatment Workflow from the Department of Health Research should be adapted. (32).
3. Surveys and surveillance studies in communities are required. (33).
4. Community involvement: Researchers should instill trust in the places where such study is planned. Studies should be coordinated with local governments. Health-care systems. Individuals identified as having a health condition as part of the screening and/or research program should have access to appropriate care. Participant engagement should go beyond the traditional individual informed consent and incorporate means for sharing results to individuals and groups. All study should identify and evaluate community issues, interests, needs, and risk tolerance.
5. Environmental evaluations should be performed, which should include a study of the water supply, food, and exposure to heat, metals, and agrochemicals.
6. Implementation of a population-level initiative to discover common health risks in a certain community, such as CKDu (34).

Early detection is easily done by these steps in a possible way which helps in preventing the prognosis of the disease in a particularly high prone population.

**CLINICAL MANAGEMENT AND TREATMENT**

 Cardiovascular morbidities, diabetes, hypertension, anemia, and peripheral vascular disease are all related with CKD. These problems complicate CKD care by making the patient more uncomfortable (35). The traditional treatment is the inhibition of RAAS pathway at various levels. Pharmaceutical firms have previously established three strategies: inhibition of angiotensin converting enzyme (ACE), competitive inhibition of angiotensin II binding to cell-surface receptors, and inhibition of the enzymatic action of renin.

In comparison to typical antihypertensive medicines, ACE inhibitors or angiotensin II receptor antagonists delay the development of proteinuria and minimize kidney structural damage. (36).

 Monotherapy with ACE inhibitors or Angiotension receptor blockers do not completely blocks the RAAS pathway hence use of renin inhibitors can effectively blocks RAAS pathway. The discovery of oral renin inhibitor Aliskiren has a prolonged halflife and longer bio-availability and reduce the albumin/creatinine ratio by 20% have proven as a effective treatment option for CKD (37).

 Aldosterone antagonist in combination with Angiotensin II receptor blockers provide significant improvement in the treatment of CKD (38).

 Statins which are potent HMG – CoA reductase inhibitors proved to reduce albuminuria and proteinuria within 6 months after initiation of therapy (39).

 Endothelial receptor antagonists shows marked hemodynamic changes and if not the patient responeded properly, it will be given on a combination with ACE inhibitors as the research showing evidence that this pair can effectively inhibit progressive nephropathies, including renal mass ablation (40).

 Treatment with an anti-TGF- antibody normalizes proteinuria, lowers glomerulosclerosis, and lessens tubular damage when compared to ACE inhibitor alone. The primary goal of TGF- type 1 receptor kinase inhibitor is decreased procollagen 1 deposition in renal tissues (41).

 Regardless of the underlying etiology of renal failure, calcium-phosphate deposits are a frequent histological finding in end-stage kidney biopsies. A synthetic vitamin D analogue called paricalcitol decreases renal inflammation in a human proximal tubular cell line via enhancing nuclear factor-ҡb (nF-ҡb) signaling that is sequestered by the vitamin D receptor (42).

 A monoclonal antibody called rituximab specifically targets the CD20 molecule found on pre-B and mature B cells. Proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis are all brought on by the size-selective features of the glomerular capillary barrier being altered to macromolecules as a result of antibody binding to glomerular cells and/or basement membranes. Rituximab is a great alternative for treating antibody-mediated glomerulopathies, particularly membranous nephropathy and cryoglobulinaemic glomerulonephritis (43).

 In individuals with renal failure, RRT (Renal Replacement Therapies) replaces nonendocrine kidney function. RRT does not repair the endocrine problems caused by renal failure such as decreased erythropoietin and 1,25-dihydroxyvitamin D3 production. It is of two types’ hemodialysis and peritoneal dialysis. Some of the variations in globally survival results can be attributed to variations in dialysis practice patterns.

 **HEALTH CARE SYSTEM CONSIDERATIONS**

Diabetes and hypertension are the main risk factors for CKD, which is already a major global problem. It is crucial to treat CKDu since it has emerged as a problem in many parts of the world. It is most likely that a number of environmental, occupational, and societal variables are involved because there isn't solid evidence for a single cause (44). To solve the issue, a more thorough approach should be recommended, as well as more study. Although there is multiple participation and no definite explanation, the proposed causative elements are possibly avoidable. The safety steps the community should implement are

1. Provide clean drinking water (pipeborne) to reduce contributory elements such as excessive silica, strontium, fluoride, and calcium/sodium imbalance which may act as nephrotoxins.
2. To protect everyone, particularly children, from Cd exposure through passive smoking, tobacco restrictions should be strengthened.
3. Ensure proper disposal of nickel-cadmium batteries, plastics, and bottle lids.
4. Make the general public and clinicians aware of the dangers of using nonsteroid analgesics inappropriately.
5. Health education to protect the general population's health, especially farmers.
6. To limit the CKDu epidemic, provide social welfare help to impacted households.
7. Neutrophil gelatinase linked lipocalin, interleukin-18 (IL-18), and Kidney Injury molecule-1 (KIM-1) are newer biomarkers that can detect pre-renal impairment early**.**
8. Because CKDu is considered an environmental ailment as a result of global warming, interventional studies to reduce heat stress may be tremendously significant. (45).

**RECOMMENDATIONS**

 CKDu is a major worldwide health concern. Increased awareness and global collaboration in recent years have been critical in the fight to contain the pandemic. Based on variations in the incidence of CKD development among people exposed to the same environmental conditions, individual risk factors are likely to be the cause of CKDu. The simple recommendations which should be follow to contain the epidemic are as follows.

1. Maintain proper hydration: current US Army recommendations advise drinking 250 mL of water per hour while working in environments that are hotter than 32°C [80].
2. Avoid high-fructose drinks and illegally made alcohol, and restrict the use of recognized nephrotoxic medicines such as NSAIDs.
3. Increase the availability of renal biopsy, expand community CKD screening to identify early loss of renal function, and more accurately identify high-risk groups and areas.
4. Encourage interdisciplinary clinical and scientific research to better comprehend the biology of CKDu and to investigate preventive measures that could impede the disease's onset and progression. Research should also be done on potential genetic modifiers that might account for the different levels of CKDu susceptibility.
5. Promote social and political measures to increase access to clean water and decrease exposure to toxic substances and metals.
6. Utilize a cooperative approach to simultaneously evaluate clinical, epidemiological, and histology data from many global CKDu clusters to help better understand the pathogenesis (46).

**CONCLUSION**

 CKDu has been clinically defined using both novel and traditional biomarkers. Heavy metals, heat stress, agrochemicals, nephrotoxins, infections, geographic location, and socioeconomic factors all appear to have a role in the development of CKDu. Each component's significance may vary depending on the patient group, and the continuous use of both conventional and cutting-edge biomarkers will increase our understanding of this disease. In addition, there hasn't been an extensive investigation of the upstream factors as a result of the emphasis on advanced renal disease therapy and late identification. Investigations on the connection between environmental factors and CKD are necessary. Kidney tubule biomarkers will be crucial in developing a global kidney health panel that can improve diagnosis and therapy for those who are at risk for or already have renal problems, even if further study and improvement are needed. No single cause can be identified with certainty; thus, a number of environmental, occupational, and social factors are almost certainly at consideration. Additional etiological and interventional research is necessary to eliminate regional risk factors that can be prevented. Large studies that include individuals with end-stage renal disease or advanced kidney disease are still needed to better evaluate the available therapies. Governmental and non-governmental entities must conduct epidemiological survey research in order to identify etiological factors and build proactive and all-encompassing approaches to sickness prevention and treatment.

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