PREVALENCE OF CHRONIC KIDNEY DISEASE OF UNKNOWN ETIOLOGY IN INDIA

Abstract

The worldwide burden of CKD has been critical, producing a greater health impact in the last 20 years. Lately, CKD of unknown origin (CKDu) is a kind of CKD seen in rural agricultural populations, and there is no single standard cause of CKDu. All over the world, CKDu was most frequently associated with men, middle age, snake bites, illness, and exposure to agrochemicals, heavy metals, herbal drugs, and heat stress. Disease development can be successfully delayed by early identification; improved screening and care approaches are critical. Advanced biomarkers have higher sensitivity and specificity than traditional biomarkers, and they are being suggested as potential tools for early disease detection. It is essential to raise public and individual awareness of health issues to identify risk factors early and take prompt action. Creating healthcare networks is also essential for improving patient safety and quality of life. Also, further etiological and interventional exploration is demanded to exclude avoidable indigenous risk factors and develop visionary, all-encompassing disease prevention and treatment methods.

Keywords: Renal disease, Heavy metals, Agrochemicals, Renal biomarkers, Renal replacement therapy

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I. INTRODUCTION

Chronic kidney disease is characterized by structural and functional abnormalities of the kidneys induced by a 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 three 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 CKD, which do not cause by these traditional factors,is termed CKD of unknown aetiology. This is identified only in the later stages and tends to progress rapidly; ithasa high chance offatality [(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)]. several environmental factors are suspected of causing CKD of unknown aetiology, such as heavy metals, agrochemical use, mycotoxins and snake bite [(6)]. As CKD of unknown aetiology is becoming more widely recognized throughout India, specific systemic investigations and extensive epidemiologic research are needed to establish a definitive cause [(7)].

II. 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 of 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 more commonly had CKD of unknown origin [(11)].Most patients with 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)].

III. CLINICAL PRESENTATION AND DIAGNOSTIC CHALLENGES

The pace of kidney function loss varies depending upon the aetiologyand exposures and is 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 m^2	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 CKD by analysing the four main biomarkers: creatinine, potassium, urea and albuminuria [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 most circustances[17]. Lack of knowledge, lack of funding, and lack of trained physicians are the major diagnostic challenges in identifying CKDu[18].

IV. POTENTIAL CAUSES AND RISK FACTORS

The heat stress/dehydration theory states CKD is characterized by recurring mild acute renal injury caused by repeated work-related dehydration episodes as osmolarity increases due to dehydration, which activates the aldose reductase enzyme responsible for converting glucose into fructose. Fructokinase metabolism results in oxidative stress, which damages tubules [19].

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

Studies show that the elevation of Hantavirus IgG antibodiesis alsoa risk factor for developing CKDu with other known factors such as consumption of alcohol, tobacco chewing and cigarette smoking[23].

V. INVESTIGATIVE APPROACHES

Kidneys carry out their most biological processes through tubule cells and allocate their vast energy for electrolyte transport, acid-base homeostasis and endocrine functions. Kidney injury isnot only restricted to glomerular functioning alone but will result in tubular atrophy and tubulointerstitial fibrosis, commonly seen in all types of CKD [24]. As serum creatinine is considered the hallmark for measuring kidney functions, it has certain limitations. It is influenced by muscle mass, diet and tubular secretion, and only through serum creatinine measurement [25]. Hence the introduction of biomarkers in assessing kidney function greatly helps to determine the type and extent of kidney injury. The renal biomarkers are Kidney Injury Marker 1 (KIM-1), Epidermal Growth Factor (EGF), Monocyte Chemoattractant Protein 1 (MCP-1), α_1 – microglobulin (AIM), hippurate or furosemide and uromodulin [26]. These biomarkers serve as a vital tool in identifying the malfunctioning of the kidneys [27].

Saliva is a complex biological fluid; changes in its composition, such as increased salivary pH, buffer capacity, and high levels of creatinine, potassium, chloride, and 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 the saliva of CKD patients [29]. There are various benefits to 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.

VI. PREVENTION AND PUBLIC HEALTH STRATEGIES

Political, cultural, economic, and healthcare system-related variables and a lack of coordinated research and inadequate financing were recognized as important hurdles for managing CKDU in India [(31)]. Even though certain measures can be taken to improve public health.

- The formation of a multidisciplinary CKD Consortium to guide the national government's agenda for CKD research and response; members of this group should include nephrologists, epidemiologists, and environmental scientists.
- At all levels of healthcare, including primary care, health centres, and district hospitals, guidelines for clinical and diagnostic assessment and standards for referral and management of CKD should be created and disseminated by professional associations and educational institutions[(32)].
- Surveys and surveillance studies in communities are required [(33)].
- Community involvement: Researchers must build trust in the local communities to conduct such research. With local governments in mind, studies should be conducted. The traditional concept of individual informed consent should not be the only component of participant engagement; there should also be a way to communicate results to individuals and groups. A community's issues, interests, needs, and risk tolerance should be identified and evaluated for all studies.
- It is important to conduct environmental assessments, which should look at the water and food supplies and how people are exposed to heat, metals, and agrochemicals.
- To implement a population-level initiative, it is essential to identify common health risks in that particular community, such as CKDu[(34)].
  These steps easily do early detection in a possible way that helps prevent the disease's prognosis in a particularly highly prone population.

VII. CLINICAL MANAGEMENT AND TREATMENT

Cardiovascular morbidities, diabetes, hypertension, anaemia, and peripheral vascular disease are related to CKD. These problems complicate CKD care by making patients more uncomfortable[(35)].The traditional treatment is the inhibition of the 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.

ACE inhibitors, or angiotensin II receptor antagonists, reduce kidney structural damage and postpone the onset of proteinuria compared to conventional antihypertensive drugs [(36)].

Monotherapy with ACE inhibitors or Angiotensin receptor blockers does not completely block the RAAS pathway; hence, using renin inhibitors can effectively blockthe RAAS pathway. The discovery of oral renin inhibitor Aliskiren has a prolonged half-life and longer bio-availability and reduced the albumin/creatinine ratio by 20%, proving an effective treatment option for CKD [(37)].

Aldosterone antagonists, combined with Angiotensin II receptor blockers, significantly improve CKD treatment [38].

Statins, potent HMG – CoA reductase inhibitors, proved to reduce albuminuria and proteinuria within six months after initiation of therapy [39].

Endothelial receptor antagonist's show marked hemodynamic changes. If the patient is not responded properly, it will be given in combination with ACE inhibitors, as the research shows evidence that this pair can effectively inhibit progressive nephropathies, including renal mass ablation [40].

Compared to ACE inhibitors alone, anti-TGF-antibody therapy normalises proteinuria, reduces glomerulosclerosis, and lessens tubular damage. The main objective of the TGF-type 1 receptor kinase inhibitor is to reduce procollagen one deposition in renal tissues[41].

In end-stage kidney biopsies, calcium-phosphate deposits are a common histological finding regardless of the underlying cause of renal failure. Enhancing nuclear factor-κb (nF-κb) signallings equestered by the vitamin D receptor, the synthetic vitamin D analogue paricalcitol reduces renal inflammation in a human proximal tubular cell line[42].

Rituximab, a monoclonal antibody, specifically targets the CD20 molecule on pre-B and mature B cells. Rituximab is an excellent substitute for other medications for treating antibody-mediated glomerulopathy, particularly membranous nephropathy and cryoglobulinaemic glomerulonephritis[43].

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

VIII. HEALTHCARE SYSTEM CONSIDERATIONS

Diabetes and hypertension are the main risk factors for CKD, 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 several 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 likely avoidable. The safety steps the community should implement are

- Provide clean drinking water (pipe-borne) to reduce contributory elements such as excessive silica, strontium, fluoride, and calcium/sodium imbalance which may act as nephrotoxins.
- Tobacco restrictions should be strengthened to protect everyone, particularly children, from Cd exposure through passive smoking.
- Ensure proper disposal of nickel-cadmium batteries, plastics, and bottle lids.

- Make the general public and clinicians aware of the dangers of inappropriate nonsteroid analgesics.
- Health education to protect the general population's health, especially farmers.
- To limit the CKDu epidemic, provide social welfare help to impacted households.
- 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**.**
- Because CKDu is considered an environmental ailment due to global warming, interventional studies to reduce heat stress may be tremendously significant[(45)].

IX. RECOMMENDATIONS

CKDu is a major worldwide health concern. In recent years, increased awareness and global collaboration have been critical in fighting the pandemic. Individual risk factors are likely to causeCKDu based on variations in the incidence of CKD development among people exposed to the same environmental conditions. The simple recommendations which should be followed to contain the epidemic are as follows.

- Maintain proper hydration: US Army recommends drinking 250 mL of water per hour while working in hotter environments than 32°C [80].
- Avoid high-fructose drinks and illegally made alcohol, and restrict the use of recognised nephrotoxic medicines such as NSAIDs.
- Renal biopsy should be made more widely available; community CKD screening should be expanded to detect early loss of renal function; and high-risk populations and areas should be more precisely identified.
- Encourage interdisciplinary clinical and scientific research to comprehend the biology of CKDu better and investigate preventive measures that could impede the disease's onset and progression.
- Encourage social and political reforms to improve water access and reduce encounters with metals and toxic substances.
- To better understand the pathogenesis, use a collaborative approach to simultaneously evaluate clinical, epidemiological, and histology data from numerous global CKDu clusters [(46)].

X. CONCLUSION

Both novel and conventional biomarkers have been used in the clinical definition of CKDu. Infections, heat stress, agrochemicals, nephrotoxins, heavy metals, geographic location, and socioeconomic factors all contribute to the onset of CKDu.Continually using traditional and cutting-edge biomarkers will deepen our understanding of this disease. The significance of each component may change depending on the patient group. It is important to look into the relationship between environmental factors and CKD. Even though more research and development are required, kidney tubule biomarkers will be essential in creating a global kidney health panel to enhance diagnosis and treatment for people at risk for or who already have renal problems. Since no single cause can be determined with absolute certainty, various environmental, occupational, and social factors are almost certainly in play. More etiological and interventional research is required to eliminate local risk factors that can be avoided. Large studies involving people with end-stage renal disease or advanced kidney disease are still required to assess the available therapies better. Governmental and non-

governmental organisations must conduct epidemiological survey research to determine etiological factors and develop proactive and comprehensive approaches to illness prevention and treatment.

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