



REVIEW ARTICLE

The Dilemma of Chronic Kidney Disease of Unknown Origin

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Abstract

Background: Over the past two decades, cumulative increases in the prevalence of chronic kidney disease (CKD) have been observed in selected geographic areas in several countries. The etiology of this CKD cannot be attributed to known or traditional causes or risk factors, and the term chronic kidney disease of unknown etiology (CKDu) has been used to describe this entity. These regional endemic nephropathies are commonly known as CKD of unidentified cause (CKDu) or CKD of nontraditional etiology (CKDnt) and, more recently, Chronic interstitial nephritis of agricultural communities (CINAC). Unlike the traditional causes of CKD (i.e., Hypertension, Diabetes, chronic glomerulonephritis, etc), CKDu has been associated with agricultural and arid regions. Also, the socioeconomic state of those regions is key.

Objective: This review addresses the present status of the knowledge for different aspects of this regional health problem as well as summarizes available evidence on the risk factors, epidemiology, clinical features, diagnosis, treatment, and prevention of CKDu. It will also highlight the reasons why Africa should be concerned about this condition.

Materials and Methods: Using the keywords “Africa, CKD of unknown origin,” a literature search was conducted on PubMed, Scopus, and Google Scholar, focusing on the research published between 2000 and 2022.

Results: Results from the literature show that predisposition to heat stress and dehydration, subclinical rhabdomyolysis, toxins from alcoholic beverages, agrochemicals, and heavy metals all result in acute kidney injury, and repeated exposures to these factors can then cause CKDu. Earlier studies in Sri Lanka nephropathy by Nanayakkara and his team in 2014 identified that a genetic variant of SLC13A3 (sodium-dependent dicarboxylate transporter member 3) is associated with CKDu. Later research conducted in 2015 discovered KCNA10 (a voltage-gated potassium channel) also as a gene implicated in CKDu; these genetic variances were discovered to be common among the populace suffering from kidney diseases, hence suggesting that, people with these genes have a high risk of developing kidney disease.

Conclusion: Predisposition to heat stress and dehydration, subclinical rhabdomyolysis, and toxins from alcoholic beverages, agrochemicals, and heavy metals all result in acute kidney injury, and repeated exposures to these factors can then cause CKDu. Also, certain genes have been found to be associated with CKDu.

Keywords: CKD of unknown origin, heat stress, rhabdomyolysis

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Introduction

Chronic kidney disease (CKD) is a growing global health problem.^{1,2} CKD affects between 8% and 16% of the world's population and is often underestimated by patients and physicians.³ CKD is a clinical syndrome that results from

a definitive change in the function and/or structure of the kidney and is characterized by its irreversibility and slow and progressive development.⁴ The definition of CKD is essential to understanding its pathology. CKD is generally characterized by a glomerular filtration rate (GFR) of less than 60 ml/min / 1.73 m², albuminuria of at least 30

mg every 24 hours, or markers of kidney damage (eg, Hematuria or structural abnormalities such as dysplastic kidneys) that last more than 13 weeks.⁵ The pathology presents a higher risk of complications and mortality.⁴

People with CKD are at increased risk for cardiovascular disease and can develop ESRD.^{4,6} Other effects of CKD can include anemia due to the underproduction of erythropoietin (EPO). Once a CKD diagnosis is made, the next step is to determine the staging based on GFR, albuminuria, and the cause of CKD.⁵ CKD, as defined above, is classified into five (5) stages. The early stages of CKD (stages 1 and 2) are manifested by kidney damage and are generally asymptomatic; kidney function is normal, but the risk of disease progression is significant. As kidney disease worsens, kidney function begins to deteriorate (stages 3 and 4 of CKD). Renal failure or ESRD (stage 5 CKD) develops over time and renal replacement therapy is required.⁷ The main causes of CKD include diabetes, high blood pressure, chronic glomerulonephritis, chronic pyelonephritis, chronic use of anti-inflammatories, autoimmune diseases, polycystic kidney disease, Alport's disease, congenital malformations, and persistent acute kidney disease.⁴ Several sociodemographic factors contribute to an increased risk of CKD, including non-white race, low education, low income, and food insecurity. Compared to whites, African Americans and Pacific Islanders have a significantly higher risk of ESRD.⁵ This is due to the higher prevalence of diabetes, high blood pressure, old age⁷, and obesity⁵. However, there is an aspect of genetic factors.

Recently, due to its idiopathic nature, a conclusive diagnosis of CKD problems has not been made. Over the past two decades, cumulative increases in the prevalence of CKD have been observed in selected geographic areas in several countries.⁸ The etiology of this CKD cannot be attributed to known or traditional causes or risk factors, and the term chronic kidney disease of unknown etiology (CKDu) has been used to describe this entity.⁹ These regional endemic nephropathies are commonly known as CKD of unidentified cause (CKDu) or CKD of non-traditional etiology (CKDnt) and, more recently, chronic interstitial nephritis of agricultural communities (CINAC).¹⁰ However, it is more locally identified by its geographic location, for example; Sri Lankan nephropathy, Uddanam nephropathy, and endemic Mesoamerican nephropathy (MeN).¹¹ The pathology is asymptomatic and therefore does not correspond to known risk factors such as diabetes, arterial hypertension, or chronic glomerulonephritis and mainly affects young and medium-sized people from low socioeconomic groups who live in agricultural communities.¹² The condition is said to have occurred in arid regions, as demonstrated by several studies in Sri Lanka.¹³ Many of the CKDu-plagued regions lack the scalable medical infrastructure and equipment, such as dialysis systems, necessary to treat kidney dysfunction associated with generalized kidney disease.¹⁴

Pathologically, the disease appears to primarily affect the proximal tubules and the interstitium, resulting in distinctive and recognizable histopathologic and clinical features. Clinically, the disease is characterized by tubular

proteinuria, mainly β 2-microglobulinuria, and the absence of hypertension and edema. The histological appearance shows tubulointerstitial nephropathy, which indicates a possible cause of toxin. CKDu can be found more and more frequently in the agricultural regions of the world.^{15,16} In general, CKDu is more common (3: 1 ratio) in men who are typically around 40 to 60 years old and who work in agriculture.¹⁷ The cause of this form of CKD is currently unknown. Heavy metals, agrochemicals, excessive use of non-steroidal anti-inflammatory drugs as analgesics, and illegal alcohol consumption have been suggested as risk factors.¹⁵ Heavy metal toxicity, pesticide exposure, snake bites, and genetics have also been suggested as risk factors.⁹ Given that the disease has a specific geographic distribution, it is highly likely that environmental and/or genetic factors are strongly linked to the etiology and progression of the disease¹⁷. In this regard, heavy metals (cadmium [Cd], arsenic [As], and various nucleotides, including uracil [U]), increased levels of fluoride (F) in groundwater, the specific composition of groundwater, aluminium (Al), and aflatoxins.¹⁷ It is important to note that this CKD problem is not limited to a single region. It has been investigated in Sri Lanka and there are reports in the literature describing similar clinical etiologies in India, Nicaragua, Costa Rica, and other Central American countries.¹⁷ In Latin America, heat stress and dehydration are the most researched topics related to CKD risk factors. Several comprehensive reviews of the literature on MeN in Latin America have examined various routes of exposure and have found that correlations of gender, family history of CKD, water intake, and latitude with the prevalence of MeN have a high odds ratio.¹⁸

Methods

literature Using the keywords "Africa, CKD of unknown origin," a literature search was conducted on PubMed, Scopus, and Google Scholar, focusing on the research published between 2000 and 2022.

In this review, we have incorporated 52 original studies, 2 systematic reviews, 6 narrative reviews/editorials, and 2 documents.

Historical Perspectives and Theoretical Framework

Epidemiology and Global Implications

The prevalence of CKD varies widely throughout the world, as does its evidence; and treatment varies.¹⁹ It is prevalent in low-income rural societies in the tropics.^{20,21,22} CKDu's geographic access points include El Salvador, Bulgaria, Guatemala, Mexico, Nicaragua, Croatia, Egypt, Serbia, India, and Sri Lanka.^{8,19} as shown in Figure 1. In Central America, it is one of the main causes of hospitalizations and deaths, mainly among young male sugarcane workers.^{19,23} The true burden of this disease is not well documented due to surveillance limitations and a lack of consensus on diagnostic criteria or case definitions.²⁴ Less is known about the epidemiology of CKD in sub-Saharan Africa in general due to the rarity of kidney biopsies and insufficient general reporting.^{8,25} However, increasing global warming, agricultural activity, and the young population pose a threat to the African community.

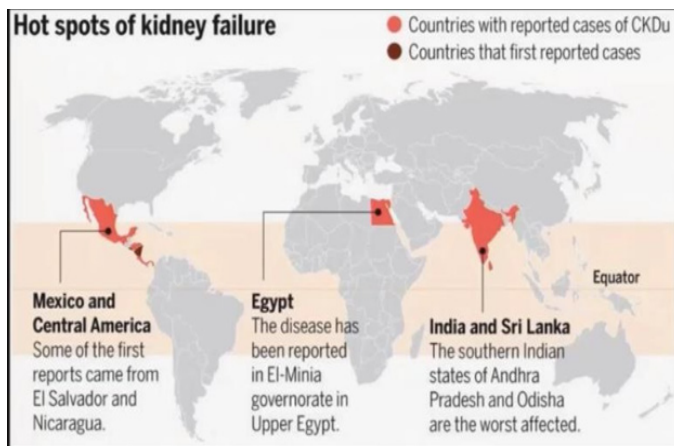


Figure 1: CKDu regional hotspots (“Home”, 2021)

Causes of CKDu and Why Africa Should Be Concerned Heat Stress and Dehydration

Recently, Central America (Mesoamerican nephropathy) has identified recurrent dehydration and heat stress as the main cause of CKD of unknown etiology epidemic.¹⁵ Rajapurkar and his team in a study conducted in India suggested that people living around hot, coastal/subcoastal, low-altitude, tropical/subtropical geographical areas are commonly affected by CKDu.²⁶ Glaser and his team in a recent study also revealed that tropical lowlands on the Pacific Coast are hot spots for Mesoamerican neuropathy. They further added that global warming in such areas has further exacerbated the condition among sugarcane farmers and has increased the prevalence of the disease.²⁷

In India, a high CKD burden has been recognized in areas where Indigenes are engaged in manual hard work under hot and humid ambient conditions.²⁷ Glaser and his colleagues also discovered that escalating levels of CKD is predominantly reported in the hottest regions in various countries²⁷; in line with this, some authors also discovered that CKD is more common among people working at sea level (high temperate areas) than sugarcane fields at higher altitudes (cooler areas).^{28,29,30,31}

Many scientists in Africa studying climate change have predicted that Africa is likely to experience higher temperatures, rising sea levels, changing rainfall patterns, and increased climate variability, all of which could affect much of its population.³² One of the serious but less researched effects of climate change is CKD.

Some scientists suggested that recurrent heat exposure with physical exertion and inadequate hydration causes recurrent AKI which then progresses over time to CKD (heat stress nephropathy). Garcia-Tobranino et al.,²⁹ in a study suggested that decreased plasma volume as a result of dehydration causes increased reabsorption of urea and other toxic waste which together with the dehydration initiates chronic kidney damage.

In addition, some authors reported that dehydration among sugarcane workers results in a decrease in their renal perfusion without structural injury. However, other authors think that an increase in creatinine levels

during work shifts may signify injury to the kidneys, and if repetitive could predispose them to develop CKD.^{33,34} Kupferman and his team estimated this to represent one-third of all cases of CKD (eGFR <60 ml per minute per 1.73m² of body surface area).³⁵

Carl-Gustaf Elinder and his colleagues in a study suggested that the reason for the high rate of dehydration observed in these sugarcane workers could possibly be because, sugarcane harvest is a work paid by piece, not by hours in Central American countries. Hence, these employees purposefully defer taking breaks and ensuring adequate hydration with the explicit objective of maximizing their earnings.³⁶ Wesselling and his team proposed that recurrent heat stress with subsequent dehydration can cause subclinical ischemic kidney injury which can later cause CKD.²⁴

The reason for higher numbers of sugarcane workers having CKD is that they often work with limited shade at environmental heat levels generally exceeding recommended limits for physical activity resulting in heat stress and dehydration which then culminates into kidney damage.^{19,24} Research in Sri Lanka revealed that prolonged sun exposure and low fluid intake were risk factors for a person developing CKD.³⁷

Heat stress and dehydration have been suggested to potentiate toxin-mediated kidney injury by enhancing the reabsorption of toxins in a state of decreased plasma volume¹⁰; other effects of heat stress, physical exertion, and dehydration that may be mechanisms of acute or chronic kidney injury include clinical or subclinical rhabdomyolysis^{28,38}, elevation in serum urate levels and urate crystalluria³⁹, release of vasopressin, and activation of aldose reductase in the kidney, with aldose reductase generating oxidative stress.^{40,41}

Dehydration which increases plasma osmolality will result in the activation of the aldose reductase pathway, converting glucose to fructose. The fructokinase in the proximal convoluted tubules of the nephron converts fructose into urates, oxidant species, and inflammatory mediators which later results in chronic kidney damage.¹⁹

Sugarcane workers laboring under the sweltering sun will further exacerbate their condition if they continuously chew the sugarcane or even hydrate with any sugary drink.⁴¹ In fact, a study on laboratory rats conducted in Mexico by Garcia and his team to investigate the effect of heat-associated dehydration on the kidneys revealed that rehydration with sugary drinks as opposed to water is associated with worse kidney damage.²⁹

Also, heat stress accompanied by severe dehydration can cause hypovolemia which will result in a decreased perfusion of the kidney and hence eventually elicit renal tubular injury ultimately leading to CKD.²⁷ Recurrent and prolonged dehydration resulting from strenuous work in tropical climates is believed to lead to subclinical acute kidney injuries that develop into chronic damage over time. Furthermore, it has been identified as a causative factor that could lead to glomerular hypertension, interstitial fibrosis, and tubular injury due to the oxidative stress exerted onto the kidneys which could be a probable pathway leading to CKDu.^{21,27}

The limitation of the heat stress hypothesis is that there are many hot regions in the world where this type of kidney disease is uncommon or has not been reported.⁴² For instance, few cases have been reported in the northern tip of Sri Lanka, even though this area is as hot as the regions with the highest frequency of disease; this might also be the lack of research in these regions. To help mitigate these problems, implementations should focus more on properly managing people at risk including screening, enhancing early detection to ensure proper treatments, minimizing exposure to nephrotoxins, etc.

In Central America, policies made focused on reducing exposures to excessive heat and improved hydration in at-risk groups.^{28,43} Many people are exposed to excessive sun rays and also engage in hard labor. This, therefore, implies that Africans are at a higher risk of CKD than non-Africans. Hence, more studies are required to investigate this crucial issue. But currently, no research shows that shows that hydration can slow the development of CKD, therefore more research should be done to evaluate this hypothesis. Africans should be concerned because dehydration is a common condition since we are exposed to excessive amounts of sunshine thereby putting us all at risk of developing CKD.

Role of rhabdomyolysis

Rhabdomyolysis is a condition characterized by injury to skeletal muscle fibers with disruption and release of their contents into the circulation. Clarkson and his team revealed in a study among marathon runners that exertional rhabdomyolysis is one of the factors responsible for the increased rate of AKI and repeated exposures to these factors can result in CKD observed in this category of people.⁴⁴

Aside from the Mesoamerican nephropathy observed among sugarcane workers, it has also been observed in farmers of other crops (eg, cotton, corn, and beans), miners, and fishermen, as well as construction workers.³¹ After they presented with symptoms of kidney damage (raised creatinine and urea levels, proteinuria, etc.), a kidney biopsy showed marked tubulointerstitial disease, often with glomerulosclerosis and evidence of kidney ischemia.⁴⁵ This condition will later progress to end-stage kidney damage.

Correa and Colleagues in research conducted in Central America revealed that CKDu mostly affects low-income, rural, and middle-aged men in agriculture or other fieldworkers requiring strenuous work.⁴⁶ Roncal-Jimenez and his team revealed that strenuous work in hot climates causes subclinical rhabdomyolysis, exacerbating hyperuricemia and urinary urate can exceed its solubility and form microcrystals.³⁹

Vanholder and his team in a paper suggested that extreme temperature is one of the major causes of rhabdomyolysis in recent times.⁴⁷ It has been well established by Glaser and his team that rhabdomyolysis can lead to AKI, and repeated exposures can result in CKDu.²⁷ Africa as a poor continent is not fully mechanized in the working space. Most of the jobs in Africa involve manual hard work. The escalation of the cost of living has precipitated a situation wherein

individuals find themselves compelled to undertake more than two employment positions concurrently as a means to address their financial needs. All these factors can therefore position Africa as a hotspot for an outbreak of CKD with time.

Toxins in Alcoholic Beverages

All metabolic wastes are excreted by the kidneys. The content of ethanol and its metabolites in urine is higher than that of blood and the liver. Chronic alcohol consumption causes decreased renal function.⁴⁸ Some studies suggest that, since the kidneys are made up of long-chain polyunsaturated fatty acids, it makes them highly sensitive to oxidative stress.⁴⁹

Research conducted by Ozbek and his team to review the induction of oxidative stress on the kidneys revealed that ethanol administration caused a significant decrease in levels of some antioxidant enzymes like catalase (CAT) and glutathione peroxidase (GSHPx) e.tc. in the kidneys of rats. Shanker and his team in a study showed that renal metabolism of ethanol via Cytochrome P450 2E1 and ADH-1(Antidiuretic hormone-1) leads to the production of oxygen species. In summary, alcohol intake results in excessive production of free radicals and a decrease in the levels of antioxidants (which confer protection against oxidative stress) in the kidneys. This can cause intrinsic kidney damage and with time can cause CKD.

Other authors suggested that the possible mechanisms alcohol can cause CKD are as follows: i. it can increase the chance of developing high blood pressure, which is the second leading cause of kidney disease, ii. Interfere with medicines making it harder to control high blood pressure. Uncontrolled high blood pressure is more likely to damage kidneys, iii. Cause more frequent urination, which can lead to dehydration prevent the kidneys from maintaining a proper balance of body fluids and minerals iv. damage kidney cells changing the structure and function of the kidneys.⁵⁰

In 1979 the World Health Organization reported in Health News that alcoholism was becoming a major problem in developing countries. Alcoholism is becoming a serious problem in Africa. According to some studies, no amount of alcohol intake is beneficial; whereas, other studies argue otherwise.^{50,51} Alcohol intake has contributed massively to disabilities, ill health conditions and death. It has been rated as the sixth most common cause of mortality and disability-adjusted life years (DALYs) among individuals globally.⁵¹

According to the WHO, drinkers in African countries consume 13% more alcohol per capita than the average among drinkers globally.⁵² With the increased rate of alcoholism among Africans, we are therefore at a high risk of developing CKD and other conditions

Agrochemicals, Heavy Metals, and Nephrotoxic Exposure

The pollution of water bodies by industrial waste and agrochemical runoff is becoming a serious threat to human lives. Due to the subsidy made by governments on all fertilizers for farmers, they sometimes overuse them way

more than what is prescribed by the Ministry of Agriculture (MOA), which later is washed off by the rains into water bodies. Chemical fertilizers are the key suppliers of heavy metals and other compounds like fluoride, nitrogen, and phosphorus to soils and water bodies. Excessive amounts of these compounds in soil will lead to bioaccumulation of them in plants and animals which indirectly affects the health of humans.⁵⁰

The consumption of water contaminated with heavy metals, fluoride, agrochemicals, and other toxins causes insidious illnesses that lead to protracted, non-communicable diseases and death²²; CKDu is one such disease that is likely to manifest. The breakout CKDu in Sri Lanka was postulated to be potentiated by many factors, including heavy metals, fluoride, cyanobacterial, algae toxins, and agrochemicals. But no specific cause has been identified for CKDu; hence the name CKD of multifactorial origin (CKDmfo) was also proposed by other scientist.²²

This therefore indicates that no single factor has been identified to be the main cause of CKDu, but the synergistic effects of a combination of factors and components, even exposure to lower amounts with yet other unidentified factors can be a cause of this (CKDu) epidemic in Sri Lanka.⁵³ Heavy metals as well as some minerals have been discovered to cause kidney injuries. Most notable among them are Cadmium and lead.⁵⁴

In addition to testing for turbidity, total dissolved substances (TDS), and total suspended particles, sophisticated water purification plants routinely test for between 40 and 90 different water contaminants. Such extensive monitoring is not considered to be practical or necessary for small-scale, community-based water purification plants, especially in developing countries.²²

In many African countries, only urban dwellers have assessed to quality water. Most of the rural communities still drink water from streams, rivers, etc. Many of these African countries are battling with the issue of illegal mining (known as Galamsey). These activities seriously contaminate our water bodies and no extensive water purifications are performed in most African countries. It, therefore, places Africa as a hot spot for the occurrence of CKDu. Hence, Africans should be concerned and should therefore allocate resources to help avert this epidemic waiting to unfold.

Genetic factors

With regards to Mesoamerican nephropathy, some authors suggested that genetic factors could account for the reason why some people develop kidney disease and others do not even though they are all exposed to the same risk factors. They further added that genetic factors could be the reason accounting for the improved conditions observed in some groups of people while others have the worst prognosis.²⁸ Nanayakkara and his team in a recent study conducted in Sri Lanka observed familial clustering in some families which suggests that CKDu could be caused by genetic factors.²¹

Earlier studies in Sri Lanka nephropathy by Nanayakkara and his team in 2014 identified that a genetic variant of SLC13A3 (sodium-dependent dicarboxylate transporter

member 3) is associated with CKDu.²¹ A later research conducted in 2015 discovered KCNA10 (a voltage-gated potassium channel) also as a gene implicated in CKDu; these genetic variances were discovered to be common among the populace suffering from kidney diseases, hence suggesting that, people with these genes have a high risk of developing kidney disease.²¹ These findings still need validation by additional studies.

Some authors have identified SLC13A3 as one of the sensitive marker genes for prognosing the clinical outcomes in type 2 diabetes mellitus patients with End Stage Renal Disease (ESRD). They further added that people with this genetic variant are at a high risk of developing hypertension, in which case if not properly managed makes kidney damage inevitable.⁵⁵

Ju and his team in a recent study using animal modules (mice) identified the SLC13A3 gene to be among other 43 genes that can be used in protein expression signatures to predict progressive renal fibrosis in mice, and hence was suggested to be a potentially useful molecular predictor for CKD progression in humans.⁵⁵ Some authors also suggested that the SLC13A3 gene plays a key role in Hg-thiol conjugates (mercury-thiol) accumulation in the renal tubules. The accumulation of inorganic mercury in the renal tubules was suggested to play a vital role in the development of CKD in humans.⁵⁶

With these alarming facts, few studies in Africa have actually focused on CKDu. Recently, there has been an increase in research worldwide in identifying genetic factors which play a key role in the development of CKDu. So far, no studies in Africa have focused on elucidating the genetic factors responsible for this disease. One possible reason might be due to a lack of adequate resources. There is a need to therefore research more on this topic since CKDu is becoming a global challenge and hence needs to be tackled with alacrity in order to avert future outbreaks.

Socio-economic Determinants

Most of the outbreaks of CKDu occurred in low-income communities. This is because, these communities are more predisposed to most of the identified risk factors associated with this condition (heat stress and dehydration, exposure to heavy metals, excessive stress, and rhabdomyolysis).

Some authors reported that CKDu occurs mostly in poorer young and middle-aged individuals in agricultural communities. And because it is progressive and asymptomatic until the late stage, a lot of people who develop this condition hardly recover.⁵⁷ Kurupparachchi and his team in a recent paper revealed that Sri Lanka's North Central region, notably the Medawachchiya District Secretariat Division of the Anuradhapura District which recorded the highest prevalence of CKDu, 80% of that population are farmers who rely on groundwater for their daily water needs.⁵⁸

Recent studies have demonstrated the association between CKDu and groundwater chemistry and the water quality in household wells^{59,60} suggesting that the disease could be caused by hydrogeochemical factors such as high fluoride and water hardness and heavy metals. Extensive monitoring of water is not considered to be practical or necessary for

small-scale, community-based water purification plants, especially in developing countries.²² This, therefore, puts these indigenous at a higher risk of developing CKDu.

Furthermore, most of these low-income communities are involved in strenuous work like farming sugarcane, rice, and a lot. Most of these farmers still rely on manual hard labor other than mechanized farming due to financial constraints. These activities mostly can cause subclinical rhabdomyolysis and if this persists may lead to the development of CKDu.

Within the African continent, the majority of the populace finds themselves positioned within the category of low-income earners. Consequently, individuals within this demographic often resort to engaging in multiple employments, surpassing the threshold of two occupations, to meet the exigencies of their daily needs. These jobs mostly involve hard labor, and they get little rest working under the scorching sun. This, therefore, predisposes them to heat stress and dehydration, subclinical rhabdomyolysis. Their risks are further compounded by the skipping of rehydration or drinking unsafe water since the prices of purified water are rising rapidly.

The aforementioned factors, therefore, point out how the poor socioeconomic status in Africa can negatively impact the health of its inhabitants. Significant but less researched in Africa is CKDu which is our main focus for this paper.

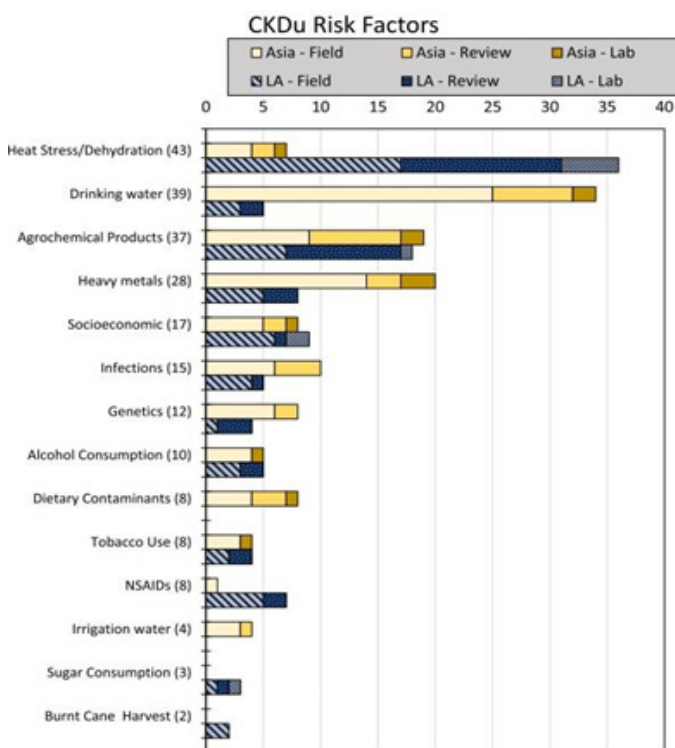


Figure. 2: Risk factors of CKDu¹⁹

Future Perspectives

CKD is a growing health burden globally with many known and unknown etiologies.¹ In high-income countries, it is most commonly associated with non-communicable diseases like diabetes and hypertension. However, in low- and middle-income countries, it has several additional

potential etiologies, such as infectious diseases and environmental toxins, but many remain unknown.^{1,61}

In this paper, the predisposition to heat stress and dehydration, subclinical rhabdomyolysis, toxins from alcoholic beverages, agrochemicals, and heavy metals all result in acute kidney injury and repeated exposures to these factors can then cause CKDu. These findings have been confirmed by several authors.^{21,27,39,50}

Also, certain genes have been found to be associated with CKDu. A study conducted in Sri Lanka to unravel the outbreak of CKDu by Nanayakkara and his team observed a familial clustering pattern of this condition.²¹ Other authors further added that genetic factors could account for the reason why some people develop kidney disease and others do not even though they are all exposed to the same risk factors.

Finally, countries with poor socioeconomic status have been discovered to record high cases of CKDu. The low-income countries are more predisposed to most of the identified risk factors associated with this condition (heat stress and dehydration, exposure to heavy metals, excessive stress, and rhabdomyolysis). Hence socioeconomic determinants have been implicated as one of the factors causing the outbreak of CKD of unknown origin worldwide.

CKDu is being reported with increasing frequency across the globe, and in many parts of Central America, Eastern Europe, and South Asia, it is being reported in epidemic proportions.^{62,63,64} Despite the increased recognition of CKDu across the globe, no studies in Africa have focused on this crucial issue. Africans should be worried because most of the factors identified above are more prevalent here in Africa and to some extent with an even higher intensity. CKDu might be the cause of most of the kidney failure cases recorded here in Africa but due to the lack of its recognition and the implementation of preventive measures in our poor healthcare state, an outbreak of this condition might be closer than ever.

The goal is to incite more research to be done on this very crucial issue to create more awareness and to also push for the implementation of the necessary measures to help avert this awaiting doom.

List of Abbreviations

ADH-1 - Antidiuretic Hormone-1

AKI - Acute Kidney Injury

CAT - Catalase

CINAC - Chronic interstitial nephritis of agricultural communities

CKD - Chronic Kidney Disease

CKDmfo - Chronic Kidney Disease of Multifactorial Origin

CKDnt - Chronic Kidney Disease of non-traditional etiology (CKDnt)

CKDu - Chronic Kidney Disease of Unknown Origin

ESRD - End Stage Renal Disease

GFR - Glomerular Filtration Rate

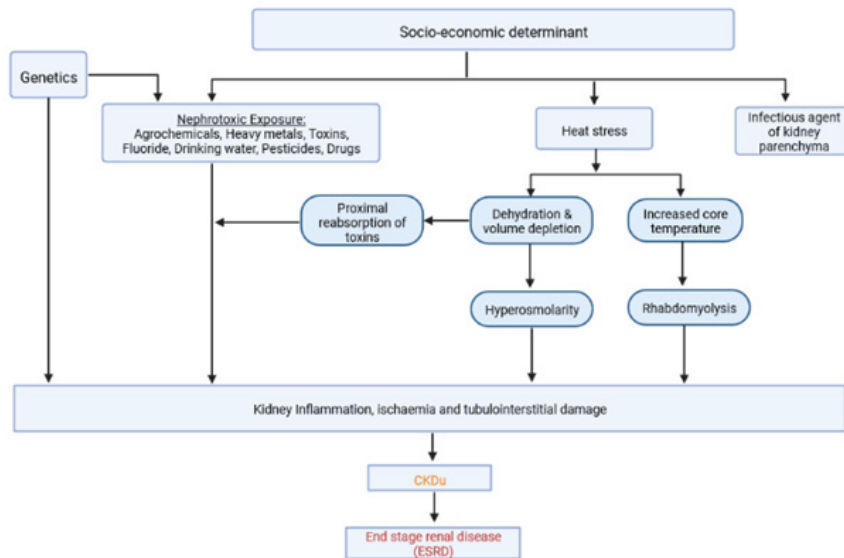


Figure. 3: Pathogenesis of CKDu (Daba, 2020)

GSHPx- Glutathione peroxidase

MeN - Mesoamerican Nephropathy

MOA - Ministry of Agriculture

TDS - Total Dissolved Substances

WHO - World Health Organization

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