

Risk of Chronic Kidney Disease among Agriculture Workers

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ABSTRACT

Background : Chronic kidney disease (CKD) is a major health concern with a growing prevalence that causes kidney failure with the consequence of unfortunate outcomes and high costs. CKD has a higher prevalence in agricultural communities, with the emergence of CKD of unknown etiology (CKDu) that affects many parts of the world especially agricultural communities. **Aim:** To highlight CKD prevalence in agriculture communities and its risk factors. Several factors like agrochemicals, environmental toxins, heat stress, contaminated water, infections, and genetic susceptibility are believed to be the cause but none of which has been proven to be the cause. **Conclusions:** CKD and CKDu prevalence is high in agriculture communities with no isolated risk factor responsible, but several factors combined could be the cause.

Keywords: CKD; Agriculture; Prevalence; Risk factors; Chronic kidney disease of unknown etiology; CKDu.

INTRODUCTION

Chronic kidney disease (CKD) is more than 3 months of impaired glomerular filtration rate (GFR) or evident kidney damage [1]. Unfortunately, CKD is irreversible, and progressive and carries a high risk of cardiovascular complications, furthermore, it's asymptomatic, and patients usually present with complications of renal dysfunction [2].

2012 Kidney Disease Improving Global Outcomes (KDIGO) KDIGO-CKD guideline updated CKD classification by adding the cause of the disease and how much albuminuria into the level of GFR (6 categories), and level of albuminuria (3 categories), together known as the (CKD-GFR-Albuminuria) CGA classification [3].

Table 1 demonstrates CGA classification with CKD prognosis [4]. This work aims to highlight CKD prevalence in agriculture communities and its risk factors.

Epidemiology of CKD

The incidence of CKD according to disease burden analysis worldwide is about 10% with 1.2 million died and 28 million affected their lives each year with CKD [5]. CKD was 27th place as the cause of death in 1990 According to the 2010 Global Burden of Disease study (death rate of 15.7 per 100,000) but rose to 18th in 2010 (annual death rate

of 16.3 per 100,000) [6]. CKD climbed the list to 12th place as a cause of death globally in 2017 [5]. **Risk factors of CKD:** A small number of cases of CKD caused by gene defects, but the risk increases with family history by multifactorial genetic factors because if a subject has a first-degree relative with end-stage kidney disease (ESKD) the risk of CKD increases 1.3 times and 10.4 times if 2 relatives are affected. It's difficult to consider ethnic group as a risk factor on its own due to its linkage to socioeconomic state, but some studies show for example that African Americans and Native Americans had a higher prevalence of ESKD in contrast to white Americans. The incidence and prevalence of CKD are affected by the socioeconomic state due to educational, environmental, and income status, in the United Kingdom (UK) there is a significant increase of 40% in the incidence of CKD if you are in the lower income group, and 86% increase in United states of America (USA) if you are from the same group. The incidence of CKD increases with age and becomes common in the elderly, the above 70 years age group represents about 46% of CKD patients [7, 8]. This can be caused by normal aging with loss of nephrons, one study estimates 6207 glomeruli could be lost each year [1]. Women are suffered more from CKD, women are predominant in CKD stage 3 to 5 groups [7]. Studies have different outcomes

in this area but the most reliable finding is that the prevalence of CKD is greater in women than men with men had greater prevalence of ESKD this can be caused by rapid progression to ESKD in men due to multiple risk factors but researches can be short in this area [1]. Increased risk of CKD is associated with Low high-density lipoprotein (HDL) cholesterol and high triglyceride levels as shown in the study by evidence of albuminuria. Also, abdominal obesity through an increased waist circumference of more than 102 cm in males and 88 cm in females can increase the risk of CKD by 2 folds [9].

Causes of CKD

Hypertension: Hypertension is known as it can be caused by CKD and hypertension can cause or progress of CKD to ESKD as an independent factor [1].

Diabetes mellitus (DM): About 40% of patients with DM will progress to CKD, so DM still the most common cause of CKD in both developed and developing countries, which makes screening of patients with DM is necessary by checking their GFR and urine albumin creatinine ratio each year, good glycemic control and early treatment of comorbidities especially hypertension with drugs that protect kidneys like angiotensin-converting enzyme inhibitors or angiotensin receptors blockers with sodium-glucose co-transport 2 (SGLT2) inhibitors can greatly slow CKD development [1].

Glomerulonephritis: It is inflammation and injury of the glomerulus which can be primary or secondary in origin and can be caused by many conditions commonly immune-mediated with the exact process still not fully understood, and the most common worldwide glomerulonephritis primary in origin is immunoglobulin A nephropathy [1].

Genetic diseases: CKD which is caused by monogenic diseases despite its importance is still undervalued as it can cause up to 70% of ESKD in children and about 10-15% overall prevalence of ESKD in adults [10].

Cardiovascular disease: CKD can be a major risk factor for CVD, and in contrast, CVD can be a major risk for CKD this overlapping relationship can be confusing when determining the cause, and for this reason an appropriate analysis of the cause needed to effectively put preventive measures to prevent disease progress [11].

Nephrotoxins: kidneys are susceptible to different kinds of substances that have the ability to harm them known as nephrotoxins many are prescribed and others are found in the food or even in the environment, the risk of these substances depend on

the number of factors including how toxic is the substance, renal susceptibility, patient condition and compartment of the kidney involved, and this can cause a syndrome like acute kidney injury (AKI), nephrotic syndrome, tubular necrosis. or can cause CKD [12].

Herbs: CKD can be caused by various herb compounds like aristolochic acid-containing herbal remedies, natural/complementary product adulterants, and heavy metal exposure to compounds like lead [12].

Water: Kidney function and kidney damage can be influenced by water in various ways. For example, low water intake daily can increase the risk of kidney function decline, Water can also damage the kidneys if it contains substances that are toxic to the kidney, such as heavy metals and organic compounds from polluted soil or water. Some water-borne diseases or infections that affect the digestive system and lead to hemolytic uremic syndrome can also increase the risk of CKD [8, 13] Urological conditions: Many urological conditions can progress to CKD by damaging the kidney and causing AKI by either predisposing to recurrent infection like vesicourethral reflux, which affects children, or through mechanical obstruction of the urinary tract by prostatic hypertrophy, renal calculi or malignancies [1].

Acute kidney injury: AKI is a recognized complication of a variety of conditions that affect the kidneys and can cause initiation or even progression of CKD by residual damage or fibrosis with time, and people who experience AKI have a high risk of developing CKD or even ESKD after recovery, [1].

Multisystem diseases: Systemic diseases can affect the kidneys in multiple ways and lead to CKD for example multiple myeloma, systemic lupus, and sarcoidosis [1].

Chronic kidney disease of unknown etiology: A new renal disease has emerged in recent years has the name CKDu and hence name the cause is still unknown, but it seems to have a special character as it does not follow the classic distribution of CKD in age group or has an obvious link to other comorbid diseases as DM and hypertension but the common link is it seems to occur in agriculture community [14].

Chronic Kidney Disease Complications

Hypertension: Hypertension is one of the chief complications of CKD and it is responsible for further progression of CKD and cardiovascular complications with increased mortality. Optimal treatment is crucial to prevent further complications like stroke or heart failure, treatment strategies

include a diet with salt restriction and weight loss and drugs that lower blood pressure [15].

Cardiovascular disease (CVD): Complications of CVD are the chief reason for death in CKD patients in many ways, CVD can increase mortality by 8.1 folds at CKD grade 5 compared to normal subjects [4, 15]. The atherosclerosis increases in CKD patients, it's found that coronary atherosclerosis is present in up to 30% of ESKD patients, [16], as well as cardiovascular complications and related mortality are predominantly from other than atherosclerosis like left ventricular abnormality with diastolic and systolic Dysfunction, valvular disease and arterial calcification, which causes cardiac arrhythmia, heart failure and even sudden death [15, 17].

Anemia: Anemia is common in ESKD as a result of erythropoietin deficiency with functional iron deficiency and its presence contributed to cardiac abnormality in CKD with increased mortality [16].

CKD-related mineral bone disorder (CKD-MBD): KDIGO defines The syndrome of CKD-MBD [18], bone and minerals metabolism is altered in CKD patients which complicates skeletal and cardiovascular systems. Bone, kidneys, intestine, and parathyroid hormone (PTH) are responsible for keeping calcium in its range and the regulation of phosphorus is slower than calcium and not as sharp as for calcium. with failure of kidneys calcium and phosphorus levels will be disturbed, causing CKD-MBD in the form of osteodystrophy, and its significance is increased risk of fracture 4 times compared to normal people, soft tissue calcification prevents complications [15, 19]. CKD-MBD specific cardiac complex syndrome is a disorder that affects the heart in ways that are not fully clear. [20].

Sodium and water imbalance: When the GFR is low, these mechanisms are impaired and can lead to hyponatremia, hypernatremia, or plasma volume overload, especially in the presence of other conditions such as heart failure or liver disease. these abnormalities are associated with high mortality [21].

Metabolic acidosis and electrolyte disorders: CKD often leads to metabolic acidosis, which happens when the body produces or consumes more acid than the kidneys can remove. This condition may not cause low plasma bicarbonate levels in the early stages because of buffering and renal adaptation. However, it can still have negative effects on muscle, hormones, bone, and kidney health. [15]. CKD patients can have hypo or hypernatremia, even if they drink enough water. This is mainly because their kidney cannot adjust the urine

concentration or dilution well [22]. Potassium imbalances are also common in advanced kidney disease. Patients are more prone to hyperkalemia than hypokalemia [22].

Uremia: uremia is a serious condition that occurs when the kidneys fail to remove uremic substances from the blood. It can be life-threatening without treatment. People with ESKD can use dialysis to extend their lives, but dialysis is not a perfect solution. It does not completely prevent the accumulation of uremic toxins, which are harmful organic compounds that worsen kidney and heart diseases [23].

CKD Prevalence in Agriculture Communities
According to global burden of disease study worldwide, incidence of CKD is about 10%, the incidence is different from a region to another [24] several studies worldwide had shown CKD prevalence in agricultural communities, like a survey on adults in three agriculture regions in El Salvador at 2009, which shows the prevalence and risk factors of CKD in 775 people aged 18 years or older, the results showed increased prevalence of CKD with 17.9% [25]. Another cross-sectional study carried out in El Salvador on 664 subjects with no exclusions, which shows CKD among sugarcane workers is about 20.2% to 28.9%, depending on location [26]. In Nicaragua a 2009 review of CKD epidemiology, highest CKD prevalence was found in sugarcane and banana plantations, and in mining regions. Young men had the most cases (3.1% to 38.1%). CKD was less common in coffee farmers and service providers. The studies showed a link between CKD and working in agriculture occupation [27]. In Indonesia the CKD prevalence among male farmers as they are the main workers involved in rice farming, revealed that the prevalence of CKD among male farmers was 24.9%, which is higher than local CKD prevalence estimates [28].

Chronic Kidney Disease and Agriculture Workers

A phenomenon of CKD among young sugarcane workers was observed by health professionals in Central America in the 1990s. The first report of this emerging health issue in the region came from El Salvador in 2002 [29]. Another mysterious CKD has been affecting rice farmers in the rural area of the North Central Province of Sri Lanka since the 1990s. The cause of the disease which was first reported in that decade remains unknown to this day [30]. The evaluation revealed that none of the patients had any of the known causes of ESKD, such as DM, hypertension, or glomerular disease. This was a remarkable finding that suggested a

different etiology for their condition [31]. In other parts of the world with hot climates. CKD is also a common health problem among rural farmers (e.g., in Tierra Blanca, Veracruz State, Mexico, where they grow crops like sugarcane, cantaloupe, papaya, and rice) [32]. According to two studies, the condition might be found in the south of Egypt and Sudan as well [33, 34].

Histopathological features: The CKD of agriculture communities has morphological features of chronic tubulo-interstitial nephritis. It is characterized by chronic damage to the tubules and interstitium of the kidney, with variable degrees of monocyte inflammation. Other changes include widespread scarring, enlarged glomeruli, some glomeruli with collapsed tufts, and abnormalities in the blood vessels outside the glomeruli, such as thickening and swelling of the inner and middle layers [35]. At 2013, a study on CKD patients in agriculture community in Salvador, found that most kidney biopsies of CKD patients reveal chronic tubulointerstitial nephritis, which is increases with advanced CKD stage in form of interstitial fibrosis accompanied by glomerular damage, and tubular atrophy [36].

CKD in Agriculture Workers Causes

Environmental toxins: The exact cause of CKD among farmers is not known, but it seems to involve multiple factors. Two possible explanations with different main causes have been suggested, one that focuses on repeated and long-term exposure to possible toxins in the workplace, the drinking water, and the environment of the farming communities [37]. Several research projects have attempted to identify the specific agents of heavy metal toxicity, such as mercury, cadmium, arsenic, and others, but the findings were inconsistent and varied across studies [38].

Agrochemical residues: Some of the most common chemicals used in farming activities around the world are pesticides and herbicides. These chemicals have been linked to AKI in animal studies, Moreover, the rise of CKD in the agriculture community in the 1990s matches the increase in pesticide use. A study by Jayasumana et al. in Sri Lanka revealed a strong link between glyphosate exposure and CKD of unknown etiology. The odds of having this type of CKD were five times higher for those who used glyphosate than for those who did not [39]. One possible mechanism of glyphosate-induced kidney damage is that glyphosate binds to metal ions such as magnesium, calcium, cadmium, strontium, and arsenic that are found in hard water and transports these harmful substances to the kidney, causing

injury to the renal proximal tubules [40]. In addition, CKD of unknown etiology affects various groups of workers, such as miners, construction workers, brickmakers, and others, who do not have occupational exposure to glyphosate or other pesticides. A systematic review and meta-analysis of epidemiological studies from 2018 also did not find a link between CKD of unknown etiology and pesticides [41, 42].

Groundwater consumption: Groundwater is the main source of drinking water for most families in regions affected by CKD with unknown etiology in the agriculture community. Jayasekara et al. used geographic information systems to show that CKD-endemic villages in Sri Lanka were often situated below the level of agricultural water sources such as reservoirs and canals. This suggests that the shallow wells in these villages might be polluted with chemicals from the water that drains from these irrigation canals [43]. Moreover, According to Jayasekara et al., drinking water from shallow wells increased the CKD of unknown etiology risk by 5 times, in contrast to using natural springs [44].

Genetic susceptibility: Some researchers have proposed that CKD of unknown etiology may have a genetic origin, based on the observation of some cases occurring within families. Two genes, SLC13A3 and KCNA10, have been found to be significantly linked to CKD of unknown etiology in the north-central provenance region of Sri Lanka, while in India, a variation in the CYP1A1 gene has been implicated [45].

Heat stress: The heat stress dehydration hypothesis, which suggests that CKD of unknown etiology in Mesoamerica is linked to the high environmental temperature is a possible explanation for the disease due to the close relationship between the two [32, 46]. When the body loses water and becomes overheated, the level of potassium in the blood can drop. This can affect the blood flow and oxygen supply to the kidney tissues, causing damage to the tubules and interstitium [47].

Infection: Some researchers have proposed that CKD of unknown etiology may be caused by leptospirosis. A systematic review of observational studies showed that people who had antibodies against *Leptospira* had lower eGFR, compared to those who did not have antibodies [48]. Parasitic infestation had been proven to cause mild and self-limited disease, but some superimposed infestations like with viruses or bacteria can cause parasitic glomerulopathy that could progress, with autoimmunity which seems to play major role in the process [49].

Multifactorial theory: A single cause for kidney disease in agriculture community is improbable, given the variation in CKD prevalence among people who share similar environmental exposures

and risk factors, A more plausible explanation is that the disease results from a complex interplay of the potential risk factors [50].

Table1: CGA classification with CKD prognosis [4].

Prognosis of CKD by GFR and albuminuria category				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30mg/g	30-300mg/g	>300mg/g
GFR categories (ml/min./1.73m ²) Description and range	G1	Normal to high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decrease	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk [4].

SUMMARY

CKD is major health concern with growing prevalence that causes kidney failure with consequence of unfortunate outcomes and high costs that burden community, CKD prevalence is rising worldwide each year, many risk factors are contributed to development of CKD include genetic factor, age, socioeconomic state, hypertriglyceridemia, and obesity. Major causes of CKD are DM, hypertension. Other causes of CKD are glomerulonephritis, genetic diseases, urological conditions, autoimmune diseases, nephrotoxic drugs, AKI, CVD and systemic diseases.

Some cases of CKD have no known cause and the condition called CKDu, which had raised prevalence in recent years and looks to be more prevalent among agriculture communities.

Many complications contributed to CKD which can be life threatening including hypertension, CVD, metabolic acidosis and electrolyte disturbance, uremia, CKD-MBD and ESKD.

CKD and CKDu prevalence seem to be higher in agriculture workers, many agriculture communities in the world looks affected with similar presentation

and histopathology finding. Many theories had been studied as agriculture workers are more exposed sun heat, agrochemicals, contaminated water supplies, infections, and environmental toxins. But none of which had been proven to be the cause.

CONCLUSIONS

CKD and CKDu has rising prevalence each year, with higher prevalence among agriculture workers, with no isolated cause determined, but many potential risk factors combined can be the reason.

Conflict of interest: None

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