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REVIEW

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Environment and chronic kidney disease in farmers

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Abstract

The prevalence of chronic kidney disease (CKD) has been on the rise worldwide. Epidemiological studies performed primarily in Central America and South Asia have reported high prevalence of CKD among young and middle-aged men working in agricultural communities. The clinical features do not appear linked to any classical CKD risk factors, such as hypertension, diabetes, or chronic nephritis. The disease develops and progresses as interstitial nephritis, without showing noticeable symptoms or high levels of proteinuria. Pathologically, the disease essentially represents chronic interstitial nephritis and is termed chronic interstitial nephritis in agricultural communities (CINAC). The potential causes of CINAC include: (1) heat stress-related factors associated with increased ambient temperatures resulting from global warming; and (2) factors connected with exposure to agrochemicals and/or pesticides. Global warming and environmental pollution will undoubtedly pose a significant health risk to farmers, and heat stress during farm work could easily result in the development and progression of CKD. Japanese agricultural regions evidently will not be spared from global environmental changes. For future epidemiological studies, researchers should establish a more comprehensive analytical method that can incorporate additional risk-factor variables, such as occupational history (including agricultural work) and ambient temperature.

Keywords: Chronic kidney disease, Dehydration, Heat stress, Farmers

Introduction

Chronic kidney disease (CKD) is primarily caused by chronic glomerulonephritis, diabetes, or hypertension. In 2017, the global prevalence of CKD was 9.1% [1]. Patients with advanced CKD require renal replacement therapy, significantly impacting their healthcare costs and quality of life. In the past, causes of CKD were often specific renal disorders such as chronic glomerulonephritis and polycystic kidney disease. However, in recent years, an increasing number of patients have initiated maintenance dialysis due to non-specific renal disorders (e.g., diabetic nephropathy and hypertensive nephropathy) associated with aging or lifestyle-related diseases [2]. Moreover, etiologies of CKD cannot even be clarified in a certain number of Japanese patients undergoing chronic dialysis [2].

Recently, environmental and occupational risk factors have drawn global attention as potential causes of CKD, promoting epidemiological studies, pathophysiological assessments, and experimental pathological verification of these risk factors. The results have revealed the prevalence of CKD not only in high-income nations, but also in low- and middle-income countries and regions. In these developing countries and regions, certain individuals without commonly known CKD risk factors (i.e., aging, hypertension, and diabetes) present with kidney injury and progress to end-stage renal failure that requires renal replacement therapy [3].

In this review article, we provide an overview of CKD and its risk factors identified from different agricultural communities around the world. I then describe the

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current knowledge about the possible mechanisms of kidney injury in farmers.

Epidemiological evidence for hot spots of chronic kidney disease in the agricultural community

Descriptive research into CKD occurring frequently in agricultural workers was initiated in 2002 in Central America [4]. In El Salvador, CKD and end-stage renal failure had been frequently observed among young workers in sugarcane fields since the 1990s, and the number of patients with these kidney diseases had been showing an increasing tendency. These patients did not exhibit any classical risk factors of CKD, such as hypertension, diabetes, or glomerular diseases. A similar phenomenon was also observed in different regions of Central America, including Costa Rica [5] and Nicaragua [6]. These kidney diseases are thus now collectively referred to as Mesoamerican nephropathy (MeN), based on the geographical features of their origins [7]. MeN is also called chronic interstitial nephritis in agricultural communities (CINAC). This is because the disease rarely shows the characteristics of glomerular injury (such as proteinuria), and is defined by its clinical features (primarily renal tubular injury) and pathological hallmarks (chronic interstitial nephritis) [8]. Sugarcane field workers tend to experience repeated episodes of acute kidney injury (AKI) that is caused, for example, by dehydration during work hours [9]. This leads to gradual decreases in renal function over the course of a harvest season, ultimately progressing to CKD. The prevalence of CKD is thus high among sugarcane farmers. In addition to sugarcane work, other types of physical labor (such as cotton farming, corn growing, and construction work) can also cause CINAC [6, 10]. A common feature associated with these occupations is long, physically intensive labor performed by young men in low-altitude farmland [11]. This suggests that the clinical conditions of CINAC patients are caused by a common mechanism involving heat-induced recurrent AKI.

Similar to MeN, CKD not attributable to any classical risk factors has frequently been identified in Sri Lanka since the 1990s [12]. Patients with this kidney disease are predominantly male and between 40 and 50 years old. Cases are initially asymptomatic and the kidney injury progresses with no increase in urinary protein levels. Pathologically, this disease is a chronic interstitial nephritis and its pathophysiology is similar to that of MeN [13, 14]. One difference between MeN and Sri Lankan nephropathy is the working environments, with patients in Central America generally working in sugarcane, cotton, and corn fields, and those in Sri Lanka mainly growing rice in paddy fields [15]. Agricultural workers in Central America and Sri Lanka are thus likely exposed to slightly different types and quantities of water pollutants (i.e., chemical agents and heavy metals) [15].

Hotspots of “CKD with no associated classical risk factors” have been reported in other regions of the world. Kidney diseases in these hotspots as well as MeN and Sri Lankan nephropathy are collectively termed CKD of unknown etiology (CKDu) [3]. In Central India, CKDu is also called “Uddanam nephropathy”, named after a typical village in the state of Andhra Pradesh. In the 1990s, chronic interstitial nephritis found in this Indian region was reported to account for a significant proportion of the clinical features of 2,028 patients with renal failure [16]. Following this first report, a systematic epidemiological study was performed [17]. Hotspots of CKDu have also been identified in Mexico [18], Egypt [19] and others shown in Table 1.

We acknowledge that CINAC exists as a clinical condition. However, a few words of caution are required when discussing its prevalence. Chronic renal dysfunction inevitably occurs with aging and thus can be regarded as one of the natural changes in physiological function [20, 21]. This is similar to the fact that arteriosclerosis is accompanied by high blood pressure. Accordingly, as the proportion of hypertensive patients increases in the elderly, the prevalence of CKD rises with age. As for the CKD studies reported from various parts of the world, an important point to note is that sample cohort sizes are usually small. Moreover, certain publications do not show the age-stratified or age-adjusted prevalence of CKD (Table 1). CKD is diagnosed based on the positive results of kidney injury and urinary protein tests, each of which is performed twice with a $\geq$ 3-month interval. However, the majority of epidemiological studies of CKDu have lacked proof of chronicity, failing to strictly differentiate between CKD and AKI [22]. Furthermore, although the diagnosis of CKD in younger patients is commonly established based on a positive proteinuria alone [23], urinalysis results have often not been included in cohort data [24]. The diagnosis of CKD can also be made based on serum creatinine levels. Creatinine is an endogenous metabolic product, and its serum levels are dependent on muscle mass. Consequently, if agricultural workers who participate in clinical studies are physically active and have a high muscle mass, researchers may overestimate the prevalence of CKD.

CKD studies reported from many different locations have shown these kinds of weaknesses in providing scientifically accurate data on prevalence, but have generally shown an increased proportion of CKD patients among young and middle-aged men in agricultural community [24].

Table 1 Original evidence of kidney disease in agricultural communities

Nation Region	Study design, participants, age	Main findings	References
El Salvador Bajo Lempa	775 individuals: 88.3% of total resident population in the region Mean age: 39 years	Prevalence of CKD was 17.9% (men, 25.7%; women, 11.8%), higher than that reported internationally	[34]
El Salvador Five communities	1184 general population without previous kidney problems 37 ± 11 years	Among men in coastal communities, 18% had eGFR < 60 mL/min/1.73 m^2 compared with 4% and 1% in communities 500 m above sea level. For agricultural workers, prevalence of reduced eGFR was highest for coastal sugarcane workers	[10]
Nicaragua Chinandega and León	194 male workers 17–39 years	Reduced eGFR occurred in 16%, 9% and 2% of sugarcane cutters, construct workers and small-scale farmers, respectively. Mean age did not differ significantly between occupations	[35]
Nicaragua León	2275 general population-based cohort Age 18–70 years	CKD prevalence was 9.1% overall; 13.8% for men and 5.8% for women. Low education level and more years of agricultural work were significantly associated with CKD	[24]
Sri Lanka Three rural areas (North Central, Central, Southern)	6153 people from random cluster sampling method, age 20–96 years	Proteinuric CKD of uncertain etiology was prevalent in the North Central area. Age, sex, occupation as a farmer, and exposure to agrochemicals were potential risk factors for CKD	[36]
India Andhra Pradesh	1184 adults through random sampling 45 ± 14 years	Prevalence of CKD 32.2%. Farmers (44.2% of subjects) showed a 20% greater prevalence of CKD compared to non-farmers in the fully adjusted model	[17]
Egypt Upper Egypt El-Minia	800 patients on renal replacement therapy Mean age, 46 years	Main occupation was farming. Unknown etiology, at 27%, was a leading cause of end-stage kidney disease	[19]
Indonesia West Java	354 healthy young Javanese rice farmers ≥ 50 years, n = 197 < 50 years, n = 157	Overall prevalences were 24.9% for CKD and 18.6% for CKDu. Odds ratio for high altitude was 2.0 (95%CI, 1.2–3.5) and longer use of insecticide and its frequency also seemed to represent risks	[37]
Mexico Tierra Blanca	579 healthy people with any occupations 42 years (IQR, 31–50 years)	Age- and sex-adjusted prevalence of low eGFR was 3.5% in the total cohort. Agriculture was the occupation with the highest adjusted prevalence of low eGFR (8.8%), associated with a > fivefold risk of low eGFR	[18]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration ratio; CKDu, CKD of unknown etiology; IQR, interquartile range

Putative etiology of occupational kidney injury related to agriculture

CINAC is defined based on the following patient characteristics [13]: (a) living or working in agricultural communities; (b) a lack of typical risk factors for CKD (including diabetes and hypertension); and (c) low levels of proteinuria. Similar to the clinical features of chronic interstitial nephritis, the kidneys in CINAC patients are small and display a thin cortex with increased echogenicity [13]. Risk factors for CKD identified to date that appear related to agricultural work include: elevated water intake, as a proxy for excessive work hours and/or heat stress [11]; high ambient temperature [25]; heavy metals in soil [3]; agrochemicals (fertilizers and pesticides) [26]; and low-quality drinking water [27] (Fig. 1). CKD is considered to progress at a different pace depending on the degree of exposure to these risk factors [13]. Perspiration from heat stress could conceivably lead to the excessive loss of body fluids (i.e., electrolyte-containing water), resulting in kidney injury. Dehydration can also potentially cause a variety of clinical conditions, including hyperuricemia and rhabdomyolysis. CINAC thus likely arises through combinations of these different pathological processes [28]. However, assuming that kidney injury is caused solely by events triggered by global warming would be unrealistic. In fact, one of the current hypotheses concerning the pathogenesis of CINAC proposes that MeN is associated with high temperatures, while agricultural chemicals are the primary cause of CKDu in South Asia. Some researchers have therefore suggested that CKDu should be called "agrochemical nephropathy", rather than "global-warming nephropathy" [29–31].

Currently, no direct evidence suggests that the development of CKD in agricultural workers is associated

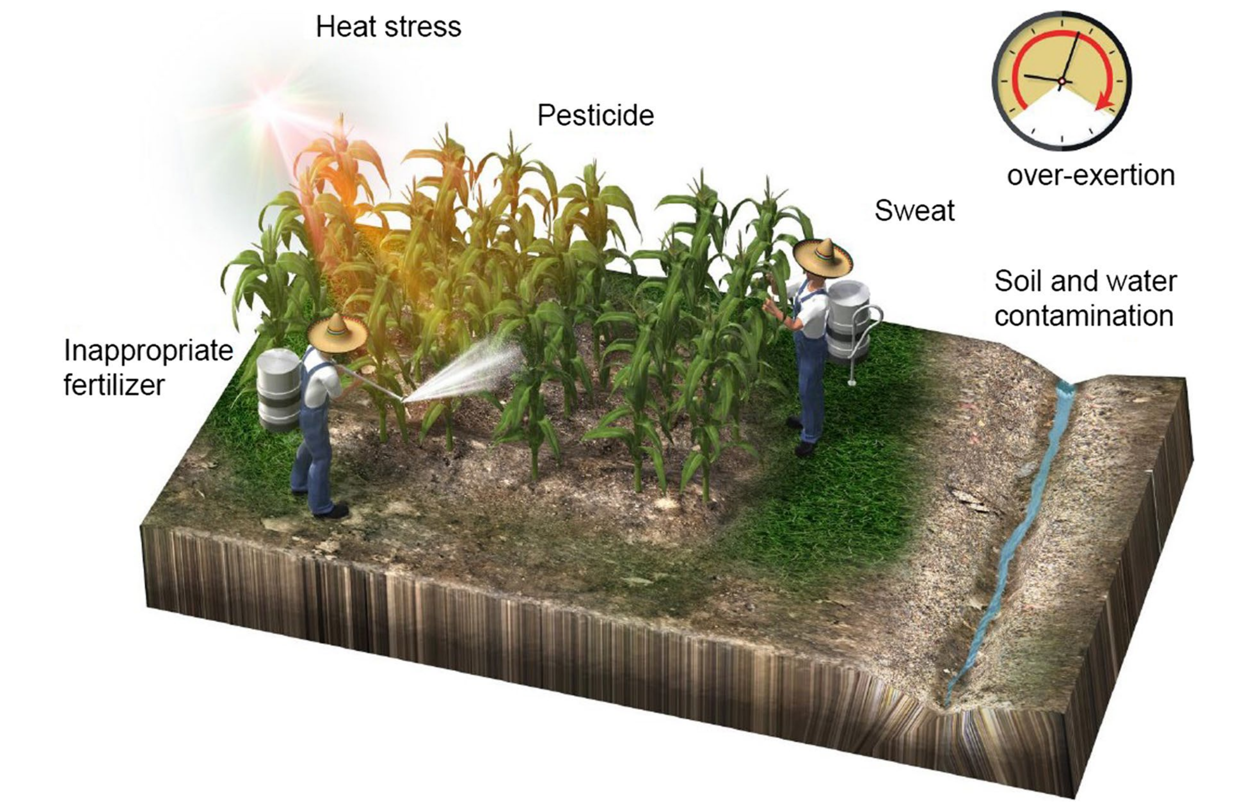

Fig. 1 Possible mechanisms for the development of kidney injury in agricultural workers. Farmers work outside, and are thus exposed to high temperatures for extended periods of time, particularly in summer. According to epidemiological studies performed in regions known to be CKD hotspots, causes of CKD include: working in the scorching sun, short breaks, inadequate quality and quantity of drinking water, and high levels of exposure to agrochemicals and pesticides. In areas where water quality is poor, easy access to surface water or groundwater suitable for drinking is not always available. This raises the concentrations of agrochemicals and pesticides remaining in the soil and increases their nephrotoxic potential

with exposure to agrochemicals, pesticides, or mixtures of both. However, pathological studies have clearly indicated that kidney injury can be caused by agrochemicals and pesticides contaminated with heavy metals or organic solvents [30]. Moreover, a recent collaborative research demonstrated 34 renal biopsies from Sri Lanka, El Salvador, India and France of patient with CINAC [8]. In addition to usual histopathology of chronic interstitial nephritis, the authors identified a unique constellation of proximal tubular cell including large dysmorphic lysosomes with a light-medium electron-dense matrix in CINAC mainly due to nephrotoxic chemicals. As this feature was also observed in renal histology of calcinurin inhibitor treated transplant patients, they suggested CINAC patients underwent a tubulotoxic mechanism similar to calcineurin inhibitor nephropathy [8]. As climate change persists, water resources (such as rivers and wells) are depleting, and this could lead to higher concentrations of agrochemicals in drinking water [32]. As a result, although the use of potentially harmful agrochemicals and pesticides has recently decreased, agricultural workers and residents in agricultural communities can still be exposed to high levels of chemical compounds that could cause CKDu [33]. Eliminating the risk of CKD thus remains a challenging task.

Need for investigating chronic kidney disease in the agricultural community

From the perspective of industrial health care, scientifically proving that certain occupations are linked to increased risks of specific types of chronic disease is important. For example, heat stress-induced renal dysfunction caused by sugarcane field labor correlates with reductions in crop yields and worker productivity [25]. The results of such analyses could be useful as a basis for the development of, for example, safety measures aimed at protecting workers from solar irradiation. Such data should also prove instrumental for managing work hours suitable for productive business operations. Regarding our society, no direct evidence has been published in Japan regarding changes in the prevalence of CKD, when this disease is considered a health problem associated with temperature increases. However, Japanese agricultural regions evidently will not be spared from global environmental changes. In this context, medical history and the results of health checkup (collectively called medical information) are insufficient for determining the etiology of CKD in previously conducted investigations. For future epidemiological studies in Japan, researchers should establish a more comprehensive analytical method that can incorporate additional risk-factor variables, such as occupational history (including agricultural work), ambient temperature and history of exposures to environmental pollutants.

Conclusion

Based on the clinical features and pathological characteristics identified in agricultural workers from CKD hotspots outside Japan, CINAC clearly represents a genuine public health issue. However, no conclusion has yet been reached regarding whether the prevalence of overall CKD is indeed higher among agricultural communities. This is partly because the epidemiological methodologies used for validating this correlation have sometimes been inadequate. The causes of CINAC include heat stress- and agrochemical-induced kidney injuries, suggesting that complex mechanisms underlie this pathogenesis. Furthermore, the main causes of CINAC appear to vary between different hotspots. In Japan, only a limited number of studies have thus far analyzed the prevalence of CKD in agricultural workers. However, Japanese agricultural regions evidently will not be spared from global warming in the future. It is desirable to practice epidemiological investigation focusing on the environment and occupation.

Abbreviations

CKD: Chronic kidney disease; CINAC: Chronic interstitial nephritis in agricultural communities; MeN: Mesoamerican nephropathy; AKI: Acute kidney injury; CKDu: CKD of unknown etiology.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The author confirms for publication.

Competing interests

The author declares that the review work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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