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Role of Organochlorine Pesticides in Chronic Kidney Diseases of Unknown Etiology

Rishila Ghosh, Manushi Siddharth,
Pawan Kuman Kare, Om Prakash Kalra and
Ashok Kumar Tripathi

Additional information is available at the end of the chapter

Abstract

Chronic kidney disease (CKD) contributes to a significant burden on the healthcare system and economy worldwide. In the last two decades, a new form of CKD: chronic kidney disease of unknown etiology (CKDu) in which the disease is not attributed to known causes has emerged as a major health issue in different geographical areas over the world mainly from farming community and has become a global concern today. Despite intense and numerous research works dedicated to CKDu, very little is known with certainty regarding its etiology and the pathophysiology behind its development. Recent evidences are emerging in favor of possible role of agrochemicals and pesticides in the pathogenesis of CKDu. Organochlorine pesticides (OCPs) due to their longer half-life and lipophilic nature persist long in the environment and are known to be biomagnified through food chain. Some study reports by the authors and a few others constitute the important body of evidences depicting the association between chronic exposures to OCPs and occurrence of CKDu through environmental contamination in farming as well as non-farming communities in different geographical areas around the globe.

Keywords: chronic kidney disease, organochlorine pesticides, end stage renal disease, eGFR, CKDu

1. Chronic kidney disease (CKD)

1.1. Overview

Chronic kidney disease (CKD) refers to a gradual and progressive decline of renal function as a result of damage to renal microstructure due to various causes ultimately leading to

end-stage renal disease (ESRD). Most, but not all forms of CKD are irreversible and progressive [1]. The progression of the disease is often silent to start with, but gradually over a period of time the disease reaches a stage in which due to increased renal damage and kidney dysfunction renal replacement therapy (RRT) in the form of dialysis or renal transplant becomes necessary to sustain life. Currently, 10% of the global population regardless of ethnic origin are affected by CKD and it has become a major burden on the healthcare system worldwide [2]. Globally, CKD is the 12th most common cause of death and 17th cause of disability [3]. It is estimated that nearly 1,00,000 new patients of end-stage renal disease (ESRD) enters RRT programs annually in India [4]. Worldwide, over two million people are on renal replacement therapy but this figure nearly represents 10% of those who need it [5]. With this alarming number, CKD has emerged as a global epidemic. The adverse outcomes like cardiovascular disease (CVD) and premature death are universal [6].

1.2. Definition and classification

Keeping in mind the global impact of CKD, a simple definition and classification was necessary for international development, dissemination, and implementation of clinical practice guideline. One such initiative was undertaken by KDIGO (Kidney Disease: Improving Global Outcomes) through one of the series of International Controversies Conferences in which, by the consensus of a large number of nephrologists worldwide, the definition and classification of CKD devised by KDOQI (Kidney Disease Outcomes Quality Initiative) was accepted with a minor modification (**Table 1**).

The National Kidney Foundation (NFK) of the United States of America classified the progression of CKD in five stages depending on the extent of renal dysfunction symptomatology and therapeutic guidelines (**Table 2**).

The term chronic renal failure applies to the reduction of significant number of functional nephron and typically corresponds to CKD stage 3–5. For obvious reason, the late stage 4 and stage 5 pose a large social, human, and economic burden. The term ESRD represents a stage in which the accumulation of toxic substances, fluid, and electrolytes which are excreted otherwise by normal kidneys produces significant clinical symptoms and even cause death unless removed from the body by renal replacement therapy in the form of kidney transplant or regular dialysis. In most of the cases but not all, patients of CKD with stage 3 or 4 progress to ESRD at a rate of 1.5% per year, whereas patients with stage 1 or 2 progress to more advanced stages approximately 0.5% per year [7].

Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without

decreased glomerular filtration rate (GFR), that can lead to decreased GFR, manifested by either:

    Pathologic abnormalities; or

    Markers of kidney damage, including abnormalities in the composition of the blood or urine; or

    Abnormalities in imaging tests

GFR < 60 mL/min/1.73m^2 for ≥3 months, with or without kidney damage

Adapted from: Levey et al. [6].

Table 1. Criteria for chronic kidney disease (CKD).

| Stages	GFR	Common features
1	≥90*	–
2	60–90*	↑ Parathyroid hormone, ↓ renal calcium reabsorption
3	30–59	Left ventricular hypertrophy, anemia secondary to erythropoietin deficiency
4	15–29	↑ Serum triglycerides, hyperphosphatemia, hyperkalemia, metabolic acidosis, fatigue, nausea, anorexia, and bone pain
5	<15	Renal failure: severe uremic symptoms

↑: increase; ↓: decrease. Adapted from: Lopez-Novoa et al. [1].*CKD is defined as either GFR < 60 mL/min/1.73m2 for 3 months or a GFR above those values in the presence of evidence of kidney damage such as abnormalities in blood or urine (e.g., proteinuria) tests or imaging studies.

Table 2. Stages of chronic kidney disease.

1.3. Etiology

Some decades ago, the leading cause of CKD was glomerulonephritis secondary to infection. Introduction of antibiotics and improved sanitary practice have changed the scenario; presently, the most common causes of CKD in adults are diabetes and hypertension in the developed world [8]. The leading causes of CKD in USA according to the 2012 US Renal Data System Annual Data Report are diabetes (49.1%), hypertension (28%), and glomerulonephritis (4.7%) [9]. As a fact, about 50% of ESRD patients in USA are diabetic and about 50–60% of all patients with CKD are hypertensive [10]. According to the CKD Registry of India, the most common cause of CKD in Indian population is diabetes (31%) followed by CKD of undetermined etiology (16%) followed by chronic glomerulonephritis (14%) and hypertensive nephrosclerosis (13%) with almost equal frequency. Other less common causes were: interstitial nephritis (7%), chronic obstructive uropathy (3.4%), miscellaneous (11.7), renovascular disease (0.8%), and graft failure (0.3%) [11] (**Figure 1**).
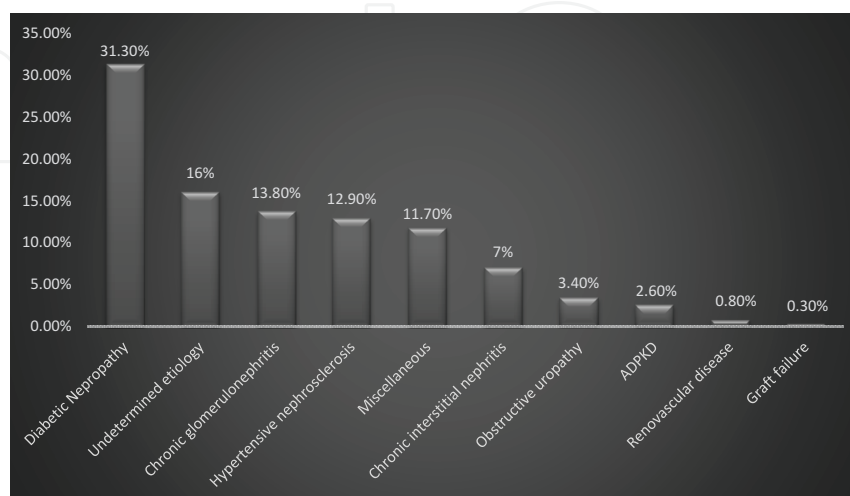
Figure 1. Etiological spectrum of Indian CKD patients of chronic kidney disease of unknown etiology (CKDu).

2. Chronic kidney disease of unknown etiology (CKDu)

2.1. Overview

In the mid of 1990s, a new form of CKD was identified among the rice paddy farmers of North Central Province (NCP) of Sri Lanka. This form of CKD is otherwise known as chronic kidney disease of unknown etiology (CKDu) [12]. Over the last two decades, similar kind of cases in significant number was reported from other farming areas of Sri Lanka and different parts of the world including Central America, among immigrants in UK from South-east Asia and India. Different terms have been used to describe CKDu in literature: chronic kidney disease of uncertain origin; chronic kidney disease of unknown origin; agrochemical nephropathy, etc. [13]. In some cases, it is named after the region or country of its origin: Central American nephropathy [14]; Salvadoran agricultural nephropathy; Mesoamerican endemic nephropathy (MeN); chronic tubulo-interstitial kidney disease of Central America; Udhanam endemic nephropathy (India); Sri Lankan agricultural nephropathy; or chronic interstitial nephritis in agricultural communities (CINAC) [15].

2.2. Global impact and epidemiological pattern

Since the first case was reported, it has become the most alarming public health issue of Sri Lanka with more than 60,000 patients and more than 20,000 deaths annually. Hospital records show a steady increase of CKDu from the year 2000 to 2015 [12]. According to the NCP (North Central Province) statistics, the cause is unknown for 2809 (70.2%) of the newly diagnosed cases of CKD and only 15.7 and 9.6% cases were diagnosed to have hypertension and diabetes, respectively. The male to female ratio was 2.6:1 showing a male preponderance. The majority of patients of CKD with undetermined etiology were in stage 4 (40%) at presentation [16].

In Central America, increasing number of CKD patients and CKD-specific mortality has been observed over the last 20 years particularly in Nicaragua and El Salvador. In the farming community of El Salvador, CKD is the fifth leading cause of death in adults. Women, men, adolescents and children, all who live in these farming communities are affected, irrespective of whether they are involved in agricultural activity or not. In Nicaragua, another endemic area for CKDu in Central America, the studies showed positive association between CKD and agricultural work, exposure to pesticides, dehydration, hypertension, drinking of *lija* (homemade liquor), and a family history of CKD [17]. Another endemic country in Central America is Costa Rica where the disease appeared in agricultural workers who work for long hours in sugarcane plantations. Clinical presentation and histopathology were consistent with chronic interstitial nephritis. The authors suspected work environment related factors to be associated with the disease [18]. A recent cross-sectional study conducted in 2009–2011 in females in agricultural communities of El Salvador, shows the prevalence of CKDu in women of these communities to be 6.7%. The key factors behind CKDu in women are probably chronic exposure to toxic agents and environmental toxins [19].

The prevalence of ESRD in Egypt's El Minia Governorate has increased from 250 to 367 per million populations from 2002 to 2007. The etiology is unknown in 27% patients [20, 21]. A case control study among ESRD patients from this area has shown association with rural residence, unsafe drinking water, family history of CKD, pesticide exposure, and medicinal plant use [21]. The authors concluded that the disease may be attributed to environmental factors.

2.3. Indian scenario

According to the report of the CKD Registry of India, of 52,273 CKD patients during 2006–2010, chronic kidney disease of unknown etiology was found in 16% of the CKD patients and was estimated to be the second leading cause only after diabetes mellitus. In this study, CKDu was more frequent in young low income patients and is clinically characterized by no or mild hypertension or proteinuria. Since there are few symptoms, disease is usually diagnosed at an advanced stage [11].

Another study from the Udhanam coastal region of Andhra Pradesh, India revealed prevalence of proteinuria to be 15.3% (54/354) in an agricultural community primarily involved in the cultivation of coconut, jackfruit, rice, and cashew with a higher prevalence in men compared to women (20% vs. 12% respectively). The prevalence of reduced GFR among males and females was 67 and 57%, respectively. The total prevalence of reduced GFR was 61% combining both males and females. Younger population showed mild to moderate proteinuria and renal histopathology studies revealed chronic tubulointerstitial nephritis. The authors suspected environmental exposure to toxic agents as the most likely cause [22]. In a recent publication by Jayasumana et al., the authors mentioned about an epidemic of CKD, not associated with the traditional risk factors from a few coastal areas of the same geographical region of Andhra Pradesh [12]. According to them, more than 4000 cases have already been diagnosed among paddy and coconut farmers of this area. The source of this information is through a personal communication with Dr. Gangadhar, Nephrologist, Nizam's Institute of Medical Sciences, Hyderabad, India [13]. No significant data of CKDu particularly among CKD patients in general population of urban or rural area are available so far.

2.4. CKDu: clinical profile and case definition

The clinical profile of CKDu patients from different geographical regions has striking similarities. Due to the slower rate of progression, majority of the affected individuals are asymptomatic for long time particularly during the early course of the disease [23]. The urine sediment shows no significant abnormalities in the markers of renal damage. Proteinuria is rare and moderate if present and can be described as "tubular" since $\beta 2$ microglobulin and other tubular markers are found to be elevated in urine [24]. In the year of 2009, Ministry of Health of Sri Lanka developed the criteria for case definition of CKDu. According to these criteria, chronic kidney disease is considered to be of unknown etiology if there is: (1) no past history of, or current treatment for diabetes mellitus or chronic or severe hypertension, snake bites, urological disease of known etiology or glomerulonephritis; (2) normal glycosylated hemoglobin level (HbA1$_C$ < 6.5%); and (3) blood pressure < 160/100 mm Hg untreated or <140/90 mm Hg on up to two antihypertensive drugs [25].

2.5. CKDu: histopathological pattern

The morphological pattern of CKDu is described as chronic tubulo-interstitial nephritis, from two of the important endemic geographical areas: Sri Lanka and El Salvador [26, 27]. The prominent findings are interstitial fibrosis and tubular atrophy with or without inflammatory monocyte infiltration. In a retrospective study of 251 renal biopsies from patients in Sri Lanka, histopathological features of the first four stages of CKDu have been described [28]. The predominant feature of stage 1 disease is mild to moderate interstitial fibrosis without the evidence of interstitial inflammation in most of the cases. Glomerulosclerosis was absent in 62.3% of the specimens. Stage 2 CKD specimens show moderate interstitial fibrosis with or without mild interstitial inflammation. Features of Stage 3 CKD had moderate to severe interstitial fibrosis, moderate inflammation, tubular atrophy, and glomerulosclerosis. In a recent study from El Salvador, more severe tubular atrophy and less glomerular lesion were found among patients of CKDu involved in sugarcane farming along with more mononuclear inflammatory infiltration when compared to non-agricultural workers [29].

2.6. CKDu: probable etiological factors

Most of the available literature points toward the exposure to environmental contaminants and agrochemicals as possible etiological factors. The countries and regions where CKDu has clustered, followed age-old practice of traditional agriculture for centuries prior to the introduction of biotechnologically produced high yield seeds, chemical fertilizers, and pesticides as a part of "green revolution" in the 1960s [30]. Interestingly, it was only after the green revolution that a high prevalence of CKD cases was reported from rural agricultural communities from the endemic areas all over the world, suggesting that a factor related to the changed agricultural practice could be a trigger to this disease [31]. Recently, evidence implicating agrochemicals, particularly fertilizers emerged in Sri Lanka, where CKDu patients were found to have higher urinary excretion of cadmium having a dose-dependent association with CKDu severity [32]. Other risk factors identified for CKDu are being a farmer, handling pesticides, drinking well water, having taken herbal or Ayurvedic medicines, etc. [33]. In a recent study, Jayasumana et al. [13] proposed a well-researched theory of renal tubular damage by heavy metals which absorbed into the body as a lattice structure formed by chelation of metal ions with glyphosate, a widely used herbicides by the farmers of the endemic area. This theory, though attractive has yet to be proven by bench research and many academic chemists do not support this view. The high prevalence of CKD in the villages located downstream [34], and among consumers of water from shallow wells [16, 35] strongly indicates the possibility of entry of toxins through contaminated drinking water [13]. Genetic susceptibility is another possible risk factor according to some studies [36].

The etiology of CKDu in Central America appears to be multifactorial. Two main hypotheses have emerged. One identifies the trigger as exposure to agrochemicals and pesticides either due to exposure during agricultural activity or through contaminated physical environment, water, and food. Occurrence of extra-renal manifestations in CKDu patients suggests generalized toxicity affecting different organ systems with renal damage being a part of systemic pathology. The second hypothesis is the effect of heat stress compounded with strenuous labor and insufficient fluid intake triggering repeated episodes of subclinical acute renal injury that could lead to chronic kidney disease [37, 38].

Available literatures on CKDu mostly show prevalence of this disease from agricultural communities of low socio-economic strata. But there is increasing concern among scientists that the health hazards of agrochemicals are no longer limited to the agricultural communities. Due to extensive and widespread contamination of food, water, soil, air, flora and fauna by environmental pollutants like OCPs, general populations not involved in agriculture and populations from non-rural area are also exposed to these toxic chemicals as well.

Agrochemicals are chemicals such as inorganic fertilizers, liming agents and acidifying agents, pesticides, plant hormones or phytohormones, and plant growth agents used to improve the production of crops. The obvious benefit of using agrochemicals is the improved production of quality and quantity of vegetables, fruits, and crops, but not without a toll. Widespread and uncontrolled use of these chemicals for long time caused extensive contamination of the environment and thus caused significant adverse effect on the ecosystem and the health of the living organisms as well as humans.

3. Pesticides

A pesticide is a substance or mixture of substances used to kill a pest. It may be a chemical substance, biological agents (such as virus or bacteria), antimicrobial, disinfectant or device used against any pest [39]. The Food and Agriculture Association (FAO) of the United Nations has defined the term pesticide as "any substance or mixtures of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of food, agricultural commodities, wood and wood product or animal feedstuffs, or substances which can be administered to animals for the control of insects, arachnids or other pests in or on their bodies." Pesticides include variety of different compounds such as insecticides, ovicides, larvicides, adulticides, herbicides, fungicides, rodenticides, etc. [40]. The use of pesticides was of great help in increasing the yield of crops in agriculture and in public health programmes for controlling vector-borne diseases. On the other hand, due to their potential toxicity to human and animals, it has become a global concern for environmental pollution and health hazard. More than 98% of sprayed pesticides and 95% of herbicides reach a destination other than their targeted species including air, water, soil, food, and non-targeted living species. Some of them are persistent organic pollutants (POPs) and contribute to significant soil contamination. In this way, they have become an integral part of the ecosystem and environment, and as they are meant for destruction of some particular species, they leave a devastating effect on other non-targeted species as well as humans leading to a potential hazard to their health [39].

3.1. Organochlorine pesticides (OCPs)

Organochlorine pesticides have a long history of indiscriminate and uncontrolled use for about five decades for both agricultural and sanitary purposes. Some of the OCPs which have been banned or restricted in the last two decades in India are shown in **Table 3**.

Others which are in main use include lindane, endosulfan, dicofol, methoxychlor, and pentachlorophenol [39]. Organochlorine pesticides (OCPs), due to their chemical stability and extremely resistant nature to degradation, persist for long in the environment (**Table 4**).

These compounds are mainly found associated with organic matter in soil and in animal tissue due to their strong lipophilic property. They bioaccumulate in the adipose tissue of animals as well as humans and even get biomagnified through food chain [41]. Increased level of different OCP residues has been detected in different human samples such as placenta, blood, semen, amniotic fluid, breast milk, etc. [42–45]. Some of the notable examples are: dichlorodiphenyltrichloroethane (DDT) and its analogues (such as methoxychlor), dicofol, aldrin, endrin, heptachlor, endosulfan, chlordane, dieldrin, lindane, mirex, etc. [39].

Compounds	Status in India	Year
Aldrin	Banned	1996
Chlordane	Banned	1996
DDT	Restricted use	1980
Dieldrin	Restricted use	1990
	Complete ban	2003
Endrin	Banned	1990
HCH	Banned	1997
Heptachlor	Banned	1996

Adapted from: Free Wikipedia, the free encyclopedia.

Table 3. Current status of organochlorine pesticides in India.

Organochlorine pesticides	Half-life in soil
α-HCH	2–8 years
β-HCH	1–7 years
γ-HCH	1.2–6.5 years
Aldrin	0.3–3.0 years
Dieldrin	2.5–8.0 years
α-Endosulfan	35–67 days
β-Endosulfan	104–265 days
p,p′-DDT	2.8–10.0 years
p,p′-DDE	1–15 years

Adapted from: Agrawal and Sharma [39] and Free Wikipedia, the free encyclopedia [49].

Table 4. Environmental half-life of organochlorines.

3.2. Exposure to OCPs

Exposure to organochlorine pesticides may occur by direct exposure through handling or spraying during agricultural activity particularly by inadequately educated farmers, without proper protective gears, by using some personal care products like lice shampoo or indirectly through contaminated food and water. Organochlorine pesticides are carried long distance via atmospheric and oceanic currents from the site of its manufacture or use and build up in the fatty tissues of animals [46]. Many studies have linked OCP exposure with consumption of contaminated animal products, mostly meat, fish, and marine mammals [47, 48]. Fetuses and children may get exposed to pesticides *in utero* as well as through breast milk [49]. Even after replacement of organochlorine pesticides by organophosphate, consumer products such as edible crops, fruits, and milk show substantial levels of organochlorine pesticides residue. In a multicentric study, residues of OCPs, especially DDT and HCH have been detected in humans and in environment [50]. Before the imposition of ban, endosulfan was in extensive use in agricultural practice and this led to its occurrence in a variety of food items in India [51]. High levels of DDT and HCH have been reported in human blood, fat, and milk samples in India [52, 53]. A recent study from Punjab, India has shown p,p′-DDE as the major contaminant detected in human breast milk samples [54].

3.3. Detectable blood levels of OCPs in general population

Detectable blood levels of organochlorine pesticides (OCPs) such as DDT, DDE, HCH, endosulfan, and aldrin have been reported from different parts of the worlds like Spain, Canada, Mexico, Egypt, Pakistan and different parts of India in agro professional as well as in the non-agro professional general population. In a recent published report from Mexico, p,p′-DDE was detected in 100% of the blood samples of the participants. p,p′-DDT was detected in 41.3% of samples. β-HCH was present in 48.6% of samples and o,p′-DDT was found in only 3.3% of the samples analyzed [55]. Published data on the level of OCPs from the blood samples of general population from different parts of India have shown the presence of a number of OCPs. The OCPs levels ranged from 2.92 to 4.52 parts per billion (ppb) for α-HCH, 1.93–10.05 ppb for β-HCH, 1.69–5.33 ppb for γ-HCH, 0.03–3.32 ppb for aldrin, 1.97–2.77 ppb for dieldrin, 0.01–2.21 ppb for α-endosulfan, 1.18–1.49 ppb for β-endosulfan, 0.045–1.62 ppb for p,p′-DDT, and 2.18–4.26 ppb for p,p′-DDE [56]. High serum concentration of BHC and DDE (range: 0.006–0.130 ppm for BHC and 0.002–0.033 ppm for DDE) were detected in agro and non-agro professionals in and around Madurai, India [50]. A recent publication from Punjab, India, revealed the presence of p,p′-DDE, p,p′-DDD, o,p′-DDE, and β-endosulfan at mean levels of 15.26, 2.71, 5.62, and 4.02 ng/ml, respectively, from the blood samples of the study subjects. Though statistically non-significant ($p > 0.05$), higher levels of total DDT residues were detected in non-vegetarians [54]. Higher blood levels of DDT have also have been reported earlier [57]. High blood levels of endosulfan (with highest mean concentration of 0.30 mg/kg) was detected along with other organophosphate and p,p′-DDT from agro and non-agro professionals from Pakistan [58].

3.4. Association of blood OCPs levels and pathological conditions

Cumulative data from all over the world have linked a number of pathological conditions with detectable or high blood levels of OCPs such as metabolic syndrome, hypercholesterolemia, insulin resistance, preterm labor, urogenital and breast cancer, diabetes mellitus, etc. In a recent report from Thailand, the total amount of serum p,p'-DDE concentration was found to have significant correlation with plasma glucose levels [59]. Another study from Egypt has shown significant positive association of only heptachlor residue and blood glucose level among the OCPs studied [60]. A recent study from Northern Benin, West Africa has shown consistently higher serum levels of four OCPs namely p,p'-DDE, p,p'-DDT, β-HCH, and trans-nonachlor in diabetic subjects compared to non-diabetic controls [61]. In a recent publication, β-HCH and aldrin has been shown to be significantly and positively associated with the risk of having metabolic syndrome [62]. Another report from this Institute has shown significant positive association of higher blood levels of α-HCH, β-HCH, p,p'-DDE, and o',p'-DDD from mothers of preterm birth cases as compared to term controls [63]. A significant association of high blood levels of BHC and its isomers, dieldrin, heptachlor, DDT and its metabolites have been shown with the occurrence of reproductive tract cancer among women from Jaipur, India [64]. Another report from U.S. has shown that serum concentration of β-HCH, trans-nonachlor, and dieldrin has significant association with risk for prostate cancer [65].

4. OCPs exposure and CKDu

Literatures are scarce about the role of OCPs in CKDu. A recent study from the same laboratory has reported significant negative correlation of eGFR of patients of CKD of unknown etiology with blood levels of γ-HCH ($p < 0.05$), total HCH ($p < 0.05$), aldrin ($p < 0.05$), and total pesticides ($p < 0.05$). The authors also observed a tendency to accumulate pesticides by the CKD patients with decreasing eGFR. They also demonstrated a significant association of total pesticide load with increased oxidative stress in CKD patients [56]. In a previous study by the same authors from the same laboratory showed that the increased OCP levels in CKD patients were partially dependent on GSTM1/GSTT1 polymorphism and particularly GSTM1 (−)/GSTT1 (−) genotype was more vulnerable in this regard [66]. Earlier, Rutten et al. has shown the significant higher levels of HCB and p,p'-DDE in the serum of dialysed and non-dialysed uremic patients than in controls [67].

Epidemiological studies from the endemic areas strongly suggest the role of agrochemicals and pesticides in the development of CKDu. The detectable blood levels of these persistent organic pollutants in the general population worldwide confirms chronic exposure of humans to these toxins which are known to have significant and diverse adverse effect on different organ systems including kidney. In view of the available literatures till date, it seems to be plausible that chronic exposure to OCPs have a crucial role in the development and progression of CKDu although precise underlying mechanisms and evidence-based effective preventive and therapeutic strategies remains an unmet goal till date. Future research works with improved study design should focus on this important issue and fresh body of evidences is expected to emerge more and more in the days ahead.

Acknowledgements

Author details

Rishila Ghosh[1], Manushi Siddharth[2], Pawan Kuman Kare[1], Om Prakash Kalra[3] and Ashok Kumar Tripathi[1]*

*Address all correspondence to: aktripathiucms@gmail.com

1 Department of Biochemistry, Environmental Biochemistry and Immunology Laboratory, University College of Medical Sciences (University of Delhi) and G.T.B. Hospital, Delhi, India

2 Multidisciplinary Research Unit, University College of Medical Sciences (University of Delhi) and G.T.B. Hospital, Delhi, India

3 Department of Medicine, University College of Medical Sciences (University of Delhi) and G.T.B. Hospital, Delhi, India

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