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Environmental Organic Pollutants are another Risk Factors for Chronic Kidney Diseases

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ABSTRACT

The prevalence of chronic kidney diseases **(CKD)** has increased rapidly over the last few decades in both developed and developing countries. This significant increase cannot be explained by the common causes of CKD, such as hypertension, diabetes, glomerulonephritis or obstructive nephropathy. Since the industrial revolution, many chemicals there have been introduced into our environment, which now become environmental pollutants. These chemicals may enter the human body through oral, inhalational, or transdermal routes, and are suspected to exert effects on all organ systems, including kidneys. This review will summarize the current epidemiological evidence relating environmental organic pollutants to CKD.

INTRODUCTION

Emerging numbers of reports suggest that the epidemic of chronic kidney disease **(CKD)** is not limited to common causes of this disease, such as hypertension, diabetes, glomerulonephritis or obstructive nephropathy. Research suggests that more than 1000 active compounds provoke harmful effects on human health, including renal damage [1]. In addition, many chemicals have been used for the industry and agriculture to produce the products we used and eat every day. Owing to the toxicity, many chemicals have recently been listed as persistent organic pollutants **(POPs)** in Stockholm convention and have been restricted their usage [1,2]. POPs consist of highly divergent organic compounds with the common characteristics of toxicity and resistance to environmental degradation through chemical, biological, and photolytic processes. Because of their persistence, POPs always bioaccumulate with potential significant impacts on human health and the environment [1,2].

Most of POPs are man-made via chemical synthesis and they are currently or were in the past employed as industrial chemicals, pesticides, pharmaceuticals, and solvents. [1,2]. The best-known POPs are dioxins, polychlorinated biphenyls **(PCBs),** brominated flame retardants and organo chlorine **(OC)** pesticides, such as dichlorodiphenyltrichloroethane **(DDT)**. Another group is high-volume produced chemicals used in the production of plastics, such as bisphenol A and phthalates. Many POPs are highly lipophilic and thereby accumulate in adipose tissue with a half-life from one month up to several years. Because of their wide spread use in daily life, they are measureable in the circulation in almost all individuals in the world. In addition, their persistence in the environment still produces harmful effects to us and environment even though some of POPs have already been forbidden to be used.

The mammalian kidneys are susceptible to toxic or ischemic injury because of its high rate of perfusion, active transport capabilities, and concentrating functions. The kidneys are often exposed to much higher concentrations of chemicals than are other organs. These high concentrations of chemicals may produce identifiable functional lesions and their effects are predictable and dosage dependent. However, research on how environmental chemicals affects kidney function is still limited. The objective of this review to introduce the current findings of how these chemicals are related to kidney diseases. Hopefully, it can draw more attention to encourage more research in this area.

DIOXINS AND FURANS

Synthetic halogenated aromatic hydrocarbons, including dioxins, such as polychlorinated dibenzo-p-dioxins **(PCDD)**, and furans, such as polychlorinated dibenzo-p-furans **(PCDFs)**, are ubiquitous environmental pollutants that are always found in waste products from the manufacture of pesticides, bleaching of wood pulp and waste incineration [3]. After having listed in the Stockholm Convention in 2001, PCDDs and PCDFs were forbidden to be used. However, they still exist in items or products that were manufactured prior to the ban. More importantly,

they are maintained in the environment and in living organisms, including humans, as they are highly resisted to degradation via biological processes [3]. Generally, the half-lives of PCDDs and PCDFs are long, ranging from 2–15 years [3]. As dioxins are always accumulated in animal fat, eating products comprising of meat, milk, eggs and fish is the major human exposure to dioxins [3].

Reduction of kidney function is found to be associated with moderate-to-high level exposure to dioxins. In a cross-sectional study of 1,531 healthy adults who lived near to a pentachlorophenol factory which was no longer in use, a strong monotonic inverse association between PCDD exposure and estimated GFR is found [4]. The highest quartile of toxin exposure appears to reduce estimated GFR in men and women (14.8 ml/min/1.73m^2 and a 21.5 ml/min/1.73m^2, respectively) when compared to the lowest quartile [5].

Furthermore, serum levels of three different PCDFs, (1,2,3,6,7,8-hexachlorodibenzo-p-dioxin; 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin; 2,3,4,7,8-pentachlorodibenzofuran) were found to be associated with diabetic nephropathy, as defined by the presence of microalbuminuria (albumin-to-creatinine ratio >30mg/g) or macroalbuminuria. In a study of 2,588 NHANES 1999–2004 participants with diabetes mellitus [5]. When 4 or more of the 23 chemicals were elevated the odds ratios were 7.00 (95% CI=1.80–27.20) for diabetic nephropathy and 2.13 (95%CI=0.95–4.78) for diabetes without nephropathy. A more recent study also demonstrated that 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin is one of the four chemicals associated with nephropathy. The proportion with one or more of these four dioxin-like chemicals elevated was 3.9% (unweighted n = 46) and the odds ratio (OR) for nephropathy was 7.1 [95% confidence interval (CI) 1.8–28.1]. Interestingly, the association is only strong among females (OR 17.4, 95% CI 3.4–88.6), but not among males [6]. These suggests that the kidneys in young females are more vulnerable to be affected when exposure to dioxins.

Another study of 2898 participants also demonstrated that a high serum dioxin level (defined as a PCDD/Fs level > 20 pg WHO98-TEQDF/g lipid) is associated with CKD (defined as having an e-GFR < 60 mL/min/1.73m^2 or diagnosis of CKD by a physician), independent of gender, hypertension, insulin level, uric acid level, and age. These results are compatible with the finding in an animal study that the impairment of renal function was related to the toxicity of 2,3,7,8-TCDD [7]. These studies demonstration a strong association between dioxin exposure and kidney diseases.

It is well known that the effects of dioxins are mainly facilitated by their binding to the aryl hydrocarbon receptor **(AhR)** [8]. AhR is a ligand-activated transcription factor which regulates gene expression after it binds to the dioxin response element in DNA sequences with the AhR nuclear translocation **(ARNT)** [9]. Although there is no direct evidence of how AhR is involved in CKD. However, there is some evidence of how AhR interacts with TGF-beta signaling pathway. AhR can positively regulate the expression of TGF-beta1, TGF-beta2 and latent TGF-beta-binding

protein-1 protein levels, which are important mediators for renal fibrosis and inflammation [10]. These findings suggest that AhR may represent a possible channel for Dioxin to induce renal injury.

POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyl **(PCB)** is a synthetic, organic chlorine compound derived from biphenyls. Owing to their chemical stability, including low flammability, PCB is commercially as used as coolants and insulating fluids for transformers and capacitors [11]. One of the major applications of PCBs was in carbonless copy ("NCR") paper, which even nowadays results in paper contamination. After having listed in the POP list by the Stockholm Convention in 2001, manufacture of PCB is banned worldwide. However, PCBs remain abundantly in human populations because of to their persistence in the environment, unfinished disposal, and ongoing use of PCB-containing products [10].

A study of 2,588 patients with diabetes mellitus enrolled in NHANES 1999–2004 demonstrated PCB 126, PCB 169. PCB 118 and PCB 156 are associated with diabetic nephropathy. Higher levels of exposure to PCB congeners were associated with an increased risk of diabetic nephropathy [5]. A more recent study demonstrated PCB 126, PCB 169, and PCB 156 are highly associated with nephropathy. The proportion with one or more of these four chemicals elevated was 3.9% (unweighted n = 46) and the odds ratio for nephropathy was 7.1 [95% confidence interval **(CI)** 1.8–28.1]. Interestingly, the association also is only strong among females (OR 17.4, 95% CI 3.4–88.6) [5].

Although the mechanism is unknown, the ability of PCB to alter the his tone modification may be one of cue how it affects kidney function as it is shown that PCBs induce endothelial cell inflammation through epigenetic regulation of NF-κB subunit p65 or affect early development of rats via alteringhistone modification pattern (Cassata et al., 2012; Liu et al., 2015).

POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic aromatic hydrocarbons **(PAHs)** are a group of chemicals containing multiple aromatic rings. Incomplete combustion with coal, oil, and gas, and other organic substances, such as tobacco and meat grilled over charcoal, is the major sources of PAHs [11]. Although exposure to these compounds predominantly occurs in the work environment, such as in chemical and fuel factories, the ubiquity of motorized vehicles with internal combustion engines and increased industrial activity has resulted in substantial environmental exposure, especially in urban areas [11]. Most importantly, oxidized PAHs produced by incomplete burning of carbon-based fuels are highly mutagenic and carcinogenic [12].

The relationship between PAH and kidney disease is unknown. PAH exposure may be one of the causes of Balkan endemic nephropathy, a chronic tubule interstitial disease [13]. Contamination of PAHs in drinking water has been implicated in renal parenchymal disease and urological

malignancies [14]. Urinary PAH metabolites were also associated with serum uric acid, GGT and CRP, suggesting possible impacts on kidney function in adolescents [14]. Prospective work is needed to investigate the potential long-term health consequences of these findings.

PERFLUOROALKYL ACIDS

Perfluoroalkyl acids **(PFAAs)**, synthetic organic fluorinated compounds, are widely used in various industries due to their excellent surfactant properties and thermal resistance. PFAAs have also commonly used in stain-resistant sprays for textile, paper, fire-retarding foams, non-stick cooking surfaces and food packaging [15]. Among PFAAs, perfluoro-octane sulfonic acid **(PFOS)** and perfluoro-octanoic acid **(PFOA)** have been commonly used for several decades. After having listed as one of POPs in the Stockholm convention, the utilization of PFOS was phased out in the production in the USA in 2002. The effects of previous exposure to PFAAs remain significant because of their 7–15 year half-life [15].

A study of 4,587 adults included in NHANES 1999–2000 and 2003–2008 found that serum levels of PFOA and PFOS were positively associated with CKD. Compared with those in the first quartile (<2.8ng/ml), that those with PFOA or PFOS levels in the fourth quartile (>5.9ng/ml) had a 1.73-fold and 1.82-fold higher risk of CKD (defined as GFR <60 ml/min/1.73 m^2), respectively [16]. These results suggest that higher PFC levels are associated with CKD.

Similar findings were observed in a cohort of 9,600 children aged 1–18 years. an inter quartile range elevation in serum levels of PFOA was correlated with a reduction in estimated GFR of 0.75 ml/min/1.73 m^2 [17]. Similarly, serum levels of PFOS, PFNA and PFHxS are also cross-sectionally correlated with a reduction in GFR. On contrary, the predicted serum PFOA levels at the time of enrolment were not statistically associated with GFR. These findings suggest that cross-sectional associations between PFAA and GFR might not be a cause of reduced kidney function but a consequence [17].

Finally, a study of 1,961 12–19-year-old adolescents included in NHANES 2003–2010 identified that adolescents in the highest PFOA and PFOS quartile not only had a lower eGFR, 6.84mL/min/1.73m^2 (95 % CI: 2.19 to 11.48) and 9.69mL/min/1.73m^2 (95 % CI: -4.59 to 14.78), respectively, compared to the lowest quartile, but also an increase of uric acid with 0.21 mg/dL (95 % CI: 0.056 to 0.37) and 0.19 mg/dL (95 % CI: 0.032 to 0.34), respectively [18]. These findings demonstrate that serum levels of PFAAs are associated with a reduced kidney function and increased uric acid levels in adolescents.

The studies mentioned above demonstrate a positive association between PFOS and CKD [16-18]. It is also shown that PFOS exposure induces oxidative damage in the salmon kidneys by altering the oxidative stress defense pathway [19]. Several studies also demonstrate that PFOS affects cellular functions via inducing oxidative stress, mitochondrial dysfunction, and apoptosis [19-23]. In addition, PFOS induces gene expression of Bax, p53 [20,21]. However, the pathological role of PFOS in CKD has not been explored.

PESTICIDES

Among the twelve Stockholm Convention persistent organic pollutants **(POPs)** listed in 2001, nine are organochlorine pesticides and they are aldrin, toxaphene, DDT, chlordane, dieldrin, endrin, heptachlor, mirex and hexachlorobenzene, which is also classified as an industrial chemical [1,2]. After World War II, these pesticides have been worldwide used to protect crop and control disease vector with significant success. Similar to other POPs, these pesticides are persistent in the environment for long periods as they, to a varying degree, resist biological, chemical, and photolytic degradation. Pesticides may cause both acute and delayed health effects in exposed subjects. These negative effects range from simple irritation of the skin and eyes to more severe effects such as affecting the nervous and reproductive systems [24,25]. The negative impact of these pesticides on agro-ecosystems, as well as on the environment and human health has become increasingly evident since the 1950s.

A study of 2,992 adults with diabetes mellitus enrolled in NHANES 1999–2004 found that the pesticide p,p'-DDT and pesticide metabolite heptachlor epoxide were significantly associated with total diabetes with nephropathy, with odds ratios of 2.08 (95% CI 1.06–4.11) and 1.75 (95% CI 1.05–2.93), respectively. When p,p'-DDT and heptachlor epoxide were both elevated, the odds ratio for diabetic nephropathy was 2.76 (95% CI 1.31–5.81) [26].

Another study of 320 end-stage renal disease **(ESRD)** cases diagnosed between enrolment (1993–1997) and 2011 among 55 580 male licensed pesticide applicators also demonstrated positive exposure-response trends for the herbicides alachlor, atrazine, metolachlor, paraquat and pendimethalin, and the insecticide permethrin. More than one medical visit due to pesticide use (HR=2.13; 95% CI 1.17 to 3.89) and hospitalization due to pesticide use (HR=3.05; 95% CI 1.67 to 5.58) were strongly correlated with ESRD [27]. A recent study about the relationship between ESRD among wives of licensed pesticide applicators also demonstrated that the rate of ESRD among women who did apply pesticides was significantly elevated among those who reported the highest (vs. lowest) cumulative general pesticide use (HR: 4.22; 95% CI: 1.26, 14.20), suggesting that ESRD may be associated with direct and/or indirect exposure to pesticides among farm women [28]. These findings suggest a correlation between ESRD and chronic exposure to pesticides.

Organochlorine pesticides and pesticide metabolites are known to have estrogenic, antiestrogenic or antiandrogenic activity [5]. The constitutive androstane receptor/pregnane X receptor pathway is thought to interact with the aryl hydrocarbon receptor pathway [5]. However, mechanistic study is still limited. More experiments should be done to clarify their interaction with these receptors.

BISPHENOL A

Bisphenol A **(BPA)** is an environmental toxin containing two phenolic rings with structural similarity with phenols. BPA was initially synthesized in the thirties as a synthetic estrogen [29-31] but was soon displaced by diethylstilbestrol. As an additive in plastics and resins, BPA is currently used to improve hardness, clarity, lightweight, and resistance to temperature to polycarbonate plastic and epoxy resins. However, incomplete polymerization and polymer degradation of BPA have been reported to allow BPA to leach out from food and beverage containers. Thus, exposure to BPA can occur through various routes, including ingestion, respiration, and absorption through the skin. It is known that after ingestion, BPA is conjugated with glucuronic acid in the liver where it loses and is then excreted to the intestine. Eventually, both BPA and its metabolites are excreted in urine [32-34].

A negative correlation has been observed between estimated glomerular filtration rate and the serum concentration of BPA [35]. In a study of 152 patients with CKD and 24 controls, a significant increase in plasma concentrations of BPA was observed in CKD. The highest concentration of BPA was obtained in patients with CKD (dialysis) with values of up to 6 times higher than controls without kidney disease [36].In addition, two large population studies document albuminuria in healthy individuals exposed to BPA: a study of 3,055 adults living in Shanghai, China and a study of 710 children enrolled in NHANES 2009–2010 [37,38]. Both studies showed a significant association between the highest level of BPA exposure based on urinary excretion and albuminuria. This association persisted independently of sex, diabetes, smoking status, hypertension, or CKD.

Patients receiving dialysis may exposure to BPA owing to their near daily use of dialysis tubing. This has been proven by studies that significant amount of BPA is present in the effluents of polymethylmetacrylate, cellulose, cellulose triacetate, polyester polymer, and polysulphone membranes, particularly the latter [39,40]. Elution of BPA might be enhanced from polysulfone and polyester-polymer alloy hollow fibres [40]. Some studies show that higher BPA levels are found in patients undergoing haemodialysis (5.3 ± 0.3ng/ml) and peritoneal dialysis (3.8 ± 0.2ng/ml), than in healthy controls (2.6 ± 0.1 ng/ml) (Bosch-Panadero et al., 2016; Murakami et al., 2007).

Animal study demonstratesa new type of podocytopathy induced by BPA [41-43]. In cultured mouse podocytes, BPA promotes cellular hypertrophy, reduces cellular viability, and induces apoptosis. In addition, *in vitro* exposure of podocytes to low (10nM) or high (100nM) concentrations of BPA induces the abundance of cyclin-dependent kinase inhibitor p27kip1, the TGF-β system, and collagen IV, which are involved in the pathogenesis of glomerulosclerosis. Furthermore, in these cells, BPA diminishes expression of nephrin and podocin, proteins of the filtration slits involved in the mechanisms of both proteinuria and podocyte survival. Similarly, injection of mice with 50mg/kg BPA per day for 5 weeks on mice induces hypertrophy, hyperfiltration, proteinuria, and podocytopaenia. A reduction the podocyte number due to apoptosis and mesangial are observed along with the elevated renal expression of p27kip1, TGF-β, and collagen IV.

The exact cause of BPA-induced albuminuria is unclear. The authors of above studies speculated about the possible role of oxidative stress and endothelial dysfunction to explain the findings. However, more studies should be conducted to understand the mechanism of BPA on kidney injury.

CONCLUSION

Environmental factors are an important cause of CKD, especially in the developing world. It is important to note that most environmental renal disease is in fact multi factorial. Prolonged cumulative exposure to environmental pollutants may not have any significant effect unless its presence in the body is in conjunction with age-associated decline in kidney function and other diseased conditions. They may then promote the deterioration in kidney function and progression to CKD. They may affect the endothelial dysfunction instead of alterations in the glomerular filtration barrier to produce albuminuria. Therefore, more mechanistic study of how these pollutants affect CKD to be performed. The output not only enable to understand how these pollutants affect the normal kidney function, but also provide strong evidence to support the restriction of any usage of these chemicals. Reducing exposure to environmental pollutants can effectively be attained by modifying the current regulations governing the usage of these compounds. Thus this reduction of the exposure to environmental pollutants would provide substantial economic benefits when compared to the costs incurred in preventing CKD.

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