RESEARCH ARTICLE

Environmental pollutants and diabetic kidney disease (DKD)

Ruolin Li, Xiaoyu Shu, Qifu Li, Shumin Yang

Authors' affiliations:

Department of Endocrinology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Address correspondence to: Shumin Yang, PhD (E-mail: 443068494@qq.com), Department of Endocrinology, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Street, Yuzhong District, Chongqing, China, 400016. Phone: +86-023-89011552, Fax: +86-023-89011552.

Abstract:

Diabetic kidney disease (DKD) is a common microvascular complication of diabetes. The etiology of DKD includes genetic and environmental factors. Genetics alone do not explain the high prevalence of DKD, therefore, modifiable environmental risk factors need to be identified. Many studies suggested that environmental pollutants such as persistent organic pollutants, Bisphenol A and PM2.5 play important roles in DKD development and progression. In this review, the relationships between these environmental pollutants and DKD will be discussed. Furthermore, effects of pollutants on DKD risk factors will be reviewed, including glucose metabolism, blood pressure and body weight. Several published epidemiological studies have revealed positive correlation between high blood levels of several environmental pollutants with poor renal outcomes in diabetic patients; however, those researches base the diagnosis of DKD on laboratory findings but not biopsies. On the other hand, although several basic studies revealed the nephrotoxicity of several environmental pollutants, the causal relationship between environmental pollutants and DKD still needs more experiments to explore, especially in diabetic animal models. In addition, in an open environment, the human body is affected by a variety of environmental factors, while researchers tend to study a specific environmental chemical, which makes the interactions among these pollutants unknown. In the future, studies focusing on the interactions among these environmental pollutants may provide valuable insights into the etiology of DKD. Besides, focusing on the genetics and the interaction between environment pollutants and genetic factors would shed light on the DKD susceptibility. Finally, before implementing strict regulations against specific environmental pollutants to prevent the occurrence and progression of DKD, data from high-quality diabetic population-based studies are still needed.

Keywords: diabetic kidney disease, environmental pollutants, Bisphenol A, PM2.5, persistent organic pollutants, Cadmium, Iron.

1. Diabetic kidney disease (DKD)

Chronic kidney disease (CKD) is a chronic kidney disorder with renal structure and/or function abnormalities induced by various causes. As one of the chronic kidney disease, diabetic kidney disease (DKD) is caused specifically by diabetes itself. DKD at early stages may be manifested as glomerular hyperfiltration, hypertrophy of both glomerulus and renal tubular epithelium, and microalbuminuria, followed by abnormalities in mesangium and interstitium, basement membrane thickening and macroalbuminuria, finally resulting in glomerulosclerosis and progressive loss of renal function. [1] The diagnosis of DKD is mainly depended on the presence of albumin in urine and/or a decline of estimated glomerular filtration rate (eGFR). About 20%-40% of the patients with diabetes mellitus have DKD, which is now the main reason of CKD and end-stage renal disease (ESRD) all over the world. [2] Moreover, in diabetic patients, DKD also leads to a higher mortality and higher risk of cardiovascular events such as coronary heart disease and stroke.

DKD is a complex disease resulting from combined effects of genetic and environmental factors. Although its detailed pathogenesis has not been clarified yet, poor glycemic control is the leading cause for DKD. Other risk factors also play important roles in its occurrence and progress, such as age, race, hypertension, hyperlipidemia, smoking and diabetes duration. [3] In recent decades, with the social industrialization and urbanization, environmental pollutants, existing almost everywhere have become a significant challenge to our lives, which accounts for multiple negative effects on human health.

Since environmental pollutants have been proved to be involved in the DKD development by plenty of studies, this paper aims to review the impacts of environmental chemicals or contaminants on DKD as well as on DKD risk factors (Table 1), and to discuss the underlying mechanisms.

2. Relationship between environmental pollutants and DKD

2.1. Persistent Organic Pollutants, POPs

Persistent organic pollutants (POPs), mainly referring to organochlorine compounds such as polychlorinated biphenyls (PCBS), dioxins and organochlorine pesticides, are widely used in the production of herbicides, pesticides and plasticizers, characterized by easy diffusion, difficult decomposition and persistent existence in environment. The human body can get exposed to them through food intake, air and water.

A recent study from the United States, in which 149 patients with type 2 diabetes were followed up for 30 years, showed a strong association between PCBS exposure at baseline and the increased risk of ESRD and death with confounders being adjusted, including age, sex, triglycerides, total cholesterol and blood sugar levels; Meanwhile, the exposure to organochlorine pesticides is also associated with the increased risk of death. [4]

The National Health and Nutrition Examination Survey (NHANES), from 1999 to 2004 with a large sample size, demonstrated that with the exposure level of PCBS and dioxins rises by one point in diabetics, the risk of DKD represents about sevenfold increase (defined as urinary albumin to creatinine ratio >30 mg/g). [5] In addition, a higher level of DDT is twice as risky as the

lower one to suffer from DKD. [6] Renal biopsy of arctic fox has showed extensive kidney damage caused by the exposure to POPs, however, with the mechanisms unknown. [7] A cross-sectional study revealed a positive correlation between the serum arylhydrocarbon receptor transactivating (AHRT) activity and urine albumin levels in people with diabetes. [8] A basic research also found that POPs may cause renal impairment through the constitutive androstane receptor-mediated pathway and the aryl hydrocarbon receptor (AhR) pathway, associated with promoted reactive oxygen species production, mitochondrial toxicity and extracellular matrix remodeling. [9]

Table 1. Associations between environmental pollutants and DKD

Pollutants	DKD Progression			Risk Factors of DKD			Reference
	Subject	UACR	eGFR	HbA1c	BP	Weight	
BPA	T2D, GP	↑	↓	↑	↑	↑	11-13,34,39
POPs	T2D	↑	↓	↑	↑	↑	4-6,32,37-38
PM2.5	GP	↑	↓	↑	↑	↑	17-20,33,40-41
Iron	T2D	↑	↓	Unknown	↑	↓	22,36,43
Cadmium	T2D	↑	↓	Unknown	↑	↓	27-30,35,42

T2D: type 2 diabetes; GP: General population; UACR: urine albumin creatinine ratio; eGFR: estimated glomerular filtration rate; BPA: Bisphenol A; POPs: persistent organic pollutants; DKD: diabetic kidney disease; PM2.5: particulate matter 2.5; BP: blood pressure.

2.2. Bisphenol A

Bisphenol A (BPA) is a small molecule that exists extensively in consumer products such as plastic cups, disposable tableware, plastic bags, printing paper. The majority of BPA can be excreted through the kidney, while a few remains in body. As an environmental endocrine disruptor, BPA is able to interfere with reproductive function, immune system, and induce cancer due to its binding affinity to estrogen receptors and other specific receptors. [10] Recent studies have suggested that the exposure to BPA is also closely related to DKD.

Our previous study reported the relationship between BPA and DKD. 121 patients with T2D and eGFR $\geq$ 60 mL/min/1.73 m^2 were enrolled and followed up for 6 years, results indicated that the baseline serum BPA level had a significant negative association with the annual decline percentage of eGFR, and the patients with high levels of serum BPA exhibited about a sevenfold increased risk of developing CKD compared to those with low levels, which is independent of age, T2D duration, blood pressure and blood glucose. [11] In accordance with our findings, a cohort study with the sample size about 3,000 and a study in 2009-2010 NHANES (including 710 children) also supported that people with high levels of BPA exposure

were more likely to develop microalbuminuria. [12, 13]

The mechanism of kidney damage induced by BPA was explored in basic studies, in which mice showed increased albuminuria and podocyte apoptosis after 5 weeks of continuous injection of BPA, and BPA promoted cell hypertrophy, decreased its vitality, and induced apoptosis in podocytes. [14] So the mechanism of BPA-induced glomerular injury, resulting in albuminuria, may be associated with oxidative stress-induced endothelial dysfunction. In addition, BPA may cause kidney damage through indirect pathways. Hyperuricemia is well acknowledged as an important risk factor for DKD. Our team has recently found that BPA promoted hepatic uric acid synthesis via the direct-binding activation of xanthine oxidase (XO), leading to increased serum uric acid concentration, [15] but further studies are needed to clarify the specific role of BPA-induced hyperuricemia in the DKD development.

2.3. Particulate Matter 2.5

Particulate matter with a diameter of 2.5μm or less is commonly stated as PM2.5. PM2.5, which is easy to accumulate heavy metals, nitrates, microorganisms and other components in the air due to its large specific surface area, can directly enter the alveoli of lungs and increase the risk of cardiovascular disease and death. [16] Studies have discovered that the exposure of PM2.5 increases the risk of urinary albumin and renal dysfunction. A study from the Veterans Administration Normative Aging Study (VANAS), including 669 elderly participants followed for 11 years, was to observe the association between PM2.5 exposure and eGFR changes. This study showed that average annual PM2.5 exposure negatively related to renal function, and eGFR decreased faster in participants with higher exposure of PM2.5 compared to those with lower exposure. [17] More recently, results from a large sample survey of 8.5 years' follow-up, enrolling nearly 2.5 million participants in the United States, reported that with the increase of PM2.5 exposure concentration, eGFR declined and the risk of ESRD increased. [18] Another study conducted renal biopsy of 71151 subjects in 283 cities in China to investigate the association between PM2.5 and glomerular injury, and discovered that 3-year PM2.5 high exposure was associated with the increased risk of membranous nephropathy. [19] A crosssectional study explored the relationship between PM2.5 exposure and microalbuminuria among 94 chefs and matched controls, and found that the proportion of subjects with microalbuminuria (urinary albumin/creatinine 30-300mg/g) was significantly higher in the chef group who exposed to high PM2.5 than that of the control group (85.1% vs. 22.3%,$p<0.01$). [20]

PM2.5, penetrating the respiratory barrier into the blood circulation, has a harmful effect on kidney maybe through oxidative stress and inflammatory factors. Although until now, there is no direct evidence of PM2.5 involvement in DKD, PM2.5 can be enriched with a variety of chemicals (heavy metals, POPs, etc.) which is reported to cause decreased renal function and elevated urinary albumin. So it is believed that PM2.5 exposure and DKD could be closely related. As controlling cooking fume, eliminating indoor smoking and reducing exhaust emissions can efficiently reduce PM2.5 air pollution, further illustrating the relationship between PM2.5 and DKD might be useful for DKD prevention.

2.4. Iron

Iron is an essential trace element in the human body, which plays an important role in physiological function by participating in various biochemical reactions, but iron overload will catalyze biological oxidation that is detrimental to body tissues. Although iron mainly enters the body through our daily diet, as an airborne dust pollutant, it also has an access to the body via the respiratory system. Iron deposition in the kidney was observed both in animal models and in diabetic population. [21] A large amount of researches from clinical and animal experiments have confirmed that trivalent iron ions (Fe3+) overload promotes the development of DKD. Khan et al.[22] found a significant positive correlation between serum Fe3+ level and urinary albumin/creatinine level in type 2 diabetic patients with albuminuria. A low-iron, polyphenol-enriched, carbohydrate-restricted diet can reduce the incidence of renal failure in patients with DKD and reduce the all-cause mortality. [23]

In diabetic animal models, iron deposition in vivo was positively correlated with the severity of kidney disease. [24] Iron has been proved to promote chronic renal interstitial inflammation and fibrosis in the animal models of chronic proteinuria-related kidney failure. [25] Decreasing dietary iron intake in diabetic mice models can slow the progression of proteinuria, mesangial dilation, extracellular matrix deposition and renal tubular injury, so as to prevent DKD development. Referring to the possible mechanisms, it was proved that restricting iron intake would inhibit oxidative stress by blocking renal NADPH oxidase subunits, P22 and NOX4. [26] The excessive accumulation of iron mainly leads to oxidative stress enhancement, through Fenton reaction producing a large number of hydroxyl radicals with cytotoxicity and nitric oxide resulting in high perfusion and high permeability of glomeruli. Iron overload also could be involved in the pathogenesis of the glomerular sclerosis and renal fibrosis by promoting the expression of inflammatory factors such as TGF-β. So reducing iron intake and increasing a calcium-rich diet that inhibits the absorption of ferric ions could both contribute to lower body iron content and avoid kidney injury.

2.5. Cadmium

Cadmium, a nephrotoxic metal pollutant, was widely used in industrial manufacture and disseminated in the environment, which enters the human body mainly through food and tobacco with a half-life of 15 to 30 years in the body. The associations between cadmium and increased renal tubular or glomerular injury have been found in many epidemiological studies and animal studies, especially in diabetic patients. A study from Australia showed that in diabetes, urinary cadmium levels were significantly higher in the albuminuria group than those with normal albumin creatinine ratio, and this correlation remained significant after adjustment for age, gender, BMI, smoking status, and blood pressure. [27] In a study of 800 Swedish women, a significant negative correlation was observed between urine cadmium levels and renal creatinine clearance as well as GFR. [28] In 229 patients with type 2 diabetes in China, Chen et al.[29] found that the urine β2-globulin (an indicator of proximal renal tubular function impairment) increased 3 to 4 times in patients with higher urine cadmium level. Previous studies also reported that urinary cadmium levels were significantly correlated with urinary N-acetyl-beta-glucosaminidase (NAG, one

of the potential markers of DKD). [30] In animal studies, it was proved that diabetic animals are more susceptible to cadmium-induced nephrotoxicity than non-diabetes, since the accumulation of cadmium in their kidneys is twice as much as that of the controls. After 90 days of cadmium treatment through drinking water, the level of NAG in the diabetic rats was two times higher than that in the non-diabetic group, [31] suggesting that cadmium exposure could aggravate the diabetic kidney injury.

2.6. Other Environmental Chemicals

Studies indicated that other environmental pollutants such as benzene, phthalates, perfluorinated alkyl acids, melamine, are closely associated with chronic kidney disease (CKD). However, their relationship with DKD is unclear for the lack of evidence to prove the causal relationship with urine albumin levels and DKD in diabetic patients.

3. Influence of Pollutants on DKD Risk Factors

In addition to direct contributions, environmental pollutants also affect the kidney indirectly. Environmental pollutants are reported to influence the risk factors of DKD, including plasma glucose level, blood pressure, and body weight, which could further aggravate DKD progression.

Exposure to POPs is demonstrated to be a risk factor for diabetes and obesity. [32] Exposures to PM2.5 and BPA were also shown to be associated with hyperglycemia which plays critical roles in DKD initiation. One-year PM2.5 exposure is significantly associated with increased HbA1c, and diabetes prevalence was 35% higher (95% CI: 19%, 53%) in those with higher PM2.5 exposures. [33] In the study from Wang T et al, for the highest vs. the lowest quartile of BPA exposure, the prevalence of insulin resistance was increased by 37%. [34] The exposure of cadmium was positively related to prediabetes, and furthermore participants with high blood cadmium had increased morbidity (OR = 1.44; 95% CI = 1.15-1.82) compared to those in the low cadmium group. [35] It was also proved that Iron overload played a role in the pathogenesis of diabetes through maintaining the function of pancreatic islet β-cells. [36] Taken together, exposures to environmental pollutants discussed above are associated with increased blood glucose and/or aggravated insulin resistance, but the specific mechanisms need to be further explored.

Besides hyperglycemia, high blood pressure and obesity play important roles in DKD progression as well. Valera B et al. found that higher risk of hypertension was associated with increasing DDT concentrations among participants aged 18-39 (OR = 1.42; 95% CI = 1.08-1.85). [37] Arrebola JP et al. showed that PCBs including PCB-138, PCB-153, PCB-180 were associated with hypertension in individuals with BMI>26.3kg/m^2. [38] A data based on 2003–2004 National Health and Nutrition Examination Survey (NHANES) from 1380 Americans also reported BPA exposure to be positively associated with hypertension, odds ratio for hypertension was 1.50 (95%CI = 1.12-2.00). [39] Compared to participants with the lowest BPA exposure (Quartile 1, urinary BPA concentration was less than <0.47 ng/ml), subjects with the highest BPA exposure (Quartile 4, urinary BPA concentration was more than >1.43 ng/ml) exhibited a 1.5-flod higher risk of

generalized obesity and 1.28-flod higher risk of abdominal obesity. [34] In a large prospective cohort study, the association between long-term exposure to PM2.5 and incident hypertension was demonstrated, with an even stronger association among obese participants and women younger than 65 years of age. [40] Furthermore, the risk of childhood overweight and obesity was increased by 30% and 60% with the exposure to PM2.5 during childhood. [41] A population-based study which included 5273 subjects found that the prevalence of hypertension significantly increased from 25% in the lowest tertile of urinary cadmium to 35.0% in the highest tertile. [42] In animal studies, iron restriction prevented the development of hypertension in stroke-prone spontaneously hypertensive rats compared to those without iron restriction diet which developed more severe vascular hypertrophy and renal damage. [43]

4. Summary

As DKD patients progressed to ESRD, the cardiovascular risk and all-cause mortality would increase significantly. Therefore, searching for DKD risk factors presents an important opportunity to prevent the development of the disease. Epidemiological studies have revealed positive correlation between high blood levels of several environmental pollutants with poor renal outcomes in diabetic patients; however, there's still an empty hole that if a poor renal outcome is due to an association between pollutants and diabetes or just because pollutants nephrotoxicity alone. Researches included in this review base the diagnosis of DKD on laboratory findings but not biopsies. Considering that CKD and DKD could share laboratory abnormalities, it's hard to determine if laboratory changes are due to DKD or just pollutants with nephrotoxicity; at least not without a biopsy where specific histological changes associated to DKD leading to a definitive diagnosis. On the other hand, although some basic studies revealed the nephrotoxicity of several environmental pollutants, the causal relationship between environmental pollutants and DKD still needs more experiments to explore, especially in diabetic animal models. In addition, in an open environment, the human body is affected by a variety of environmental factors, while researchers tend to study a specific environmental chemical, which makes the interactions among these pollutants unknown. In the future, studies focusing on the interactions among these environmental pollutants may provide valuable insights into the etiology of DKD. Besides, focusing on the genetics and the interaction between environment pollutants and genetic factors would shed light on the DKD susceptibility. Finally, before implementing strict regulations against specific environmental pollutants to prevent the occurrence and progression of DKD, data from high-quality diabetic population-based studies are still needed.

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