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EDITORIAL

New risk factors for obesity and diabetes: Environmental chemicals

The global prevalence of diabetes and associated metabolic diseases has increased dramatically in recent decades. The International Diabetes Federation estimates that 382 million people worldwide have diabetes (8.3% of adults), and that 592 million people (10% of adults) will have diabetes in 2035[1]. The estimated population with diabetes is greater in the Western Pacific than other regions. In Korea, the prevalence of diabetes is 12.4%, or an estimated 4.01 million people[2]. Type 2 diabetes accounts for more than 95% of the diabetes cases in Korea. Patients with diabetes and society pay tremendous medical costs for diabetes treatment and managing its complications. In 2013, global health spending on diabetes reached at least US $548 billion, and this is estimated to exceed US$627 billion by 2035[1]. Efforts to reduce the burden of diabetes involve clarification of its pathogenesis and the risk factors for diabetes. The main pathogenesis of type 2 diabetes involves β-cell dysfunction in the pancreas and peripheral insulin resistance. Factors contributing to the development of type 2 diabetes include old age, obesity, lack of physical activity, a family history of diabetes and a genetic predisposition. However, these traditional risk factors alone cannot explain the rapidly increasing prevalence of diabetes worldwide (Figure 1).

Recently, much research has examined factors beyond these conventional risk factors, including environmental chemicals, nutrients such as vitamin D and trace elements, and the intestinal microbiome. With uncontrolled industrialization, environmental pollutants have contaminated the air, water and soil. Consequently, people have been exposed to environmental chemicals unknowingly, continually, and chronically through inhalation and ingestion over the past several decades. Sometimes, chemical plant explosions or chemical weapons cause massive, acute exposure to environmental chemicals in specific regions.

In January 2011, the National Institute of Environmental Health Sciences Division of the National Toxicology Program held an international workshop to assess the data on the associations between environmental chemicals and diabetes and obesity[3]. We need to examine epidemiological and experimental evidence of the effects of environmental chemicals, including toxic metals, persistent organic pollutants (POPs) and bisphenol A (BPA; Figure 1).

For instance, there is much evidence for a relationship between heavy metals and the risk of obesity and diabetes. Arsenic is related to cancer and peripheral vascular diseases.

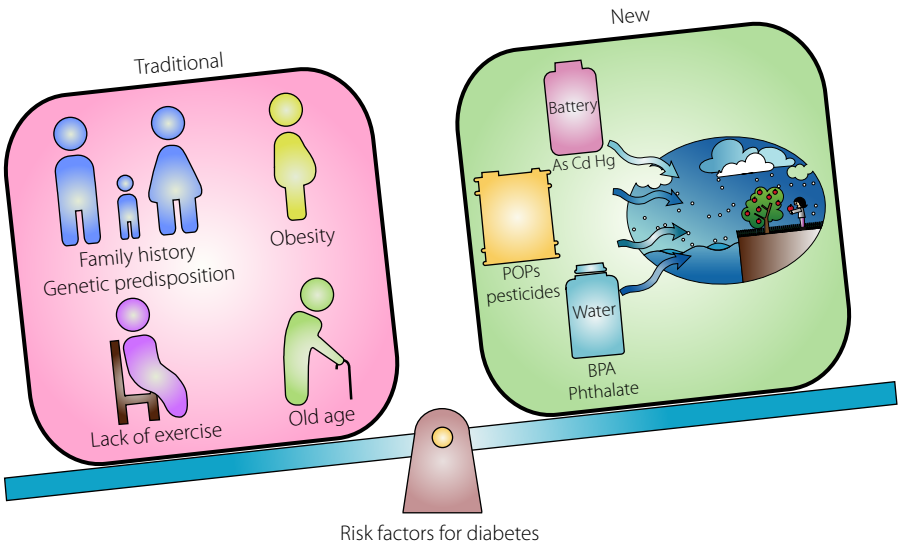

Figure 1 | Risk factors for diabetes. Environmental chemicals have contaminated the air, water and soil that are chronically exposed to people. These are considered to be the new risk factors for diabetes, and affect the pathogenesis of diabetes with traditional risk factors. As, arsenic; BPA, bisphenol A; Cd, cadmium; Hg, mercury; POPs, persistent organic pollutants.

The diabetogenic effect of inorganic arsenic has been evaluated, as the prevalence of type 2 diabetes is higher in areas with high arsenic exposure. In a prospective follow-up study, the incidence of type 2 diabetes was two- to fivefold higher in residents chronically exposed to arsenic compared with subjects living in low-exposure areas[4]. Type 2 diabetes was much more frequent in older age groups who experienced long-term arsenic exposure. Subjects who were exposed to higher cumulative arsenic levels were more obese. Arsenic might be involved in insulin resistance and β-cell dysfunction, both major components of the pathogenesis of type 2 diabetes. Oxidative stress caused by exposure to arsenic decreased glucose-stimulated insulin secretion *in vitro*[5]. In adipocytes, arsenic increased insulin resistance by suppressing the insulin signaling cascade and glucose uptake. Arsenic also inhibited adipogenic and myogenic differentiation.

Cadmium and mercury are widespread, non-degradable, toxic, heavy metals. Cadmium can interfere with calcium absorption, cause Itai-itai disease, influence glucose homeostasis and induce hyperglycemia. Cadmium disrupts pancreatic β-cells and increases insulin resistance, resulting in the reduced secretion of adiponectin and deactivated insulin signaling transduction cascades[5]. Patients with organic mercury poisoning, referred to as Minamata disease, have glycosuria[6]. Mercury-induced oxidative stress induces pancreatic β-cell death and dysfunction, and affects the insulin signaling pathway. Additional research is required to establish a relationship between heavy metals and type 2 diabetes.

Persistent organic pollutants are organic compounds that can persist and accumulate in fat tissue as a result of their lipophilicity and resistance to biodegradation. Although the use of POPs was restricted several decades ago because of potential harmful effects on human health and the environment, POPs still influence human health as a result of previous exposure. POPs include polychlorinated biphenyls, dioxin and organochlorine pesticides, such as dichlorodiphenyltrichloroethane. These were originally referred to as endocrine-disrupting chemicals, because they interfere with the functions of endocrine hormones, such as sex hormones, glucocorticoids and thyroid hormone. In a 19-year follow-up prospective study, the incidence of type 2 diabetes increased with the plasma levels of hexachlorobenzene. In a meta-analysis, the incidence of type 2 diabetes in subjects with a high total polychlorinated biphenyl plasma concentration was 1.7-fold higher than that of subjects with a low concentration[7]. Although epidemiological studies have shown positive associations between POPs and type 2 diabetes, *in vitro* and animal studies should clarify the pathogenesis and mechanisms by which POPs affect the development of type 2 diabetes and metabolic disorders. A recent study showed that rats fed a crude fish oil diet containing a low-dose POP mixture developed visceral obesity, hepatosteatosis and insulin resistance[7]. We need to consider not only the nutrient composition and daily caloric intake, but also chronic exposure to environmental chemicals that might be contained in the diet. In general, the polyunsaturated fatty acids in fish oil have beneficial effects, improving dyslipidemia in patients with diabetes, whereas POPs in fish oil elevate total cholesterol levels and aggravate insulin resistance[7]. In addition to the association between POPs and type 2 diabetes development, POPs have been linked with metabolic syndrome, which predisposes to type 2 diabetes and shares the underlying pathogenesis of insulin resistance with type 2 diabetes. In cross-sectional and prospective analyses, elderly individuals with high plasma levels of less chlorinated polychlorinated biphenyls had double or triple the risk of abdominal obesity[8]. However, there is also controversy regarding the connection between POPs and obesity. The dose–response relationship between plasma POP levels and abdominal obesity is not linear, but rather shows an inverted U-shaped. We must clarify the association between POPs and obesity.

BPA and phthalate, which are used to make many plastic products, can leach from plastic containers into foods and beverages, resulting in daily exposure. Several cross-sectional studies showed inconsistent results between BPA and phthalate and type 2 diabetes[6]. Recently, prospective cohort study reported urinary BPA and butyl phthalate were associated with type 2 diabetes[9]. BPA can affect glucose homeostasis, insulin secretion, signaling pathway in the pancreas and adipogenesis[3,9]. Phthalate is a peroxisome proliferator-activated receptors α and γ activator, and regulates the lipid and glucose homeostasis in the liver and adipose tissue[3,9].

We have discussed the environmental chemicals potentially associated with obesity and diabetes. Our attention to environmental chemicals has shifted from the effects of human carcinogens or acute exposure to their influence on metabolic disorders. Although there has been much research on environmental chemicals, investigations into their role as causal factors for diabetes are required. Lifestyle modification is a fundament aspect of diabetes prevention and management, and we must emphasize this to diabetic patients and groups at high risk of developing diabetes. Diabetes is a chronic disease that results from many risk factors. There is likely a complicated interplay between established and new risk factors, including environmental chemicals. We need to reduce the exposure to the potential risks from environmental chemicals.

In conclusion, with the explosive increase in the social burden of diabetes, we must focus on the roles of traditional risk factors in the development of type 2 diabetes, as well as those of emerging environmental chemicals that contribute to the pathogenesis of type 2 diabetes.

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Ja Young Jeon[1], Kyoung Hwa Ha[2], Dae Jung Kim[1,2,*]
[1]*Department of Endocrinology and Metabolism, Ajou University School of Medicine;* [2]*Cardiovascular and Metabolic Disease*

Etiology Research Center, Ajou University School of Medicine, Suwon, Korea
**E-mail: djkim@ajou.ac.kr*

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