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Effects of Endocrine-Disrupting Chemicals on Obesity and Diabetes

REVIEW
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ABSTRACT

The increasing incidence of obesity and type 2 diabetes mellitus (T2DM) is a global problem. Although the obesity epidemic is mostly associated with a lack of physical activity and diet, several chemicals have been demonstrated to have a potential role in its pathophysiological mechanisms. An accumulating volume of evidence indicates that a subclass of endocrine-disrupting chemicals (EDCs) can impair hormonally regulated metabolic processes, particularly in the case of exposure early in life when the defense mechanisms of the human body are yet to be fully developed. These chemicals are called "obesogenic EDCs" and might cause some people to gain weight despite their attempts to increase physical activity and limit calorie intake. Similarly, background exposure to some environmental EDCs has been associated with diabetes and impaired glucose metabolism. Certain widespread EDCs, including pesticides, dioxins, and bisphenol A, in animal models may change β function and insulin resistance. These EDCs, which may accumulate in adipose tissue and cause a pro-inflammatory response, can also be found at measurable levels in human blood and can either imitate or block some hormonal reactions. In this review, we evaluate EDCs in relation to obesity and T2DM in light of the current literature.

Keywords: Diabetes, EDC, endocrine-disrupting chemicals, metabolic syndrome, obesity

Introduction

Obesity and diabetes represent 2 of the main public health problems that have reached alarming proportions in recent years, leading to serious complications, a significant loss of function and workforce, and a substantial financial burden to the national economies. Obesity in adult and pediatric populations is considered an epidemic by the World Health Organization (WHO).[1] The prevalence of obesity has increased approximately 3 times in 50 years. As of 2016, it has been reported that 39% of adults aged 18 and over are overweight, and 13% are obese worldwide.[2] In addition, the prevalence of obesity increases, especially in early ages (children and adolescents). According to 2013 data, obesity rates in these age groups were reported as 23.8% in boys and 22.6% in girls.[3] According to TUIK's 2019 Turkey Health Survey data, the rate of obese individuals aged 15 and over was 19.6% in 2016, increasing to 21.1% in 2019.[4] Today, lack of adequate physical activity and increasing calorie consumption are the main risk factors for obesity. However, the growing obesity epidemic cannot be attributed to only energy intake and expenditure because, as in many other chronic diseases, obesity results from interactions between genetic, behavioral, and environmental factors. In 2015, a report published by the Energy Balance Measurement Working Group experts emphasized that subjective measurement of obesity and being overweight should be replaced by objective biomarkers measurement to determine adiposity because of evidenced links with obesity. Some cytokines such as visfatin, hormones including resistin or leptin, or plasma proteins such as haptoglobin are good indicators of the extent of adiposity. In addition, C-reactive protein, plasminogen activation inhibitor 1, and sialic acid have been proven to be good predictors of adiposity level. Biological markers are now being introduced because of their more accurate results than that of subjective surveys.[5]

Most people with obesity have multiple comorbidities, including type 2 diabetes mellitus (T2DM), insulin resistance, metabolic syndrome, sleep apnea, high blood pressure, gallbladder disease, and nonalcoholic fatty liver.[6] The metabolic syndrome that describes several conditions, including obesity, glucose intolerance, dyslipidemia, and hypertension, poses a high risk for developing T2DM. Individuals with metabolic syndrome have a 5-fold increased risk of developing T2DM.[6] The International Diabetes Federation estimated the number of people

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with diabetes as 537 million with a prevalence of 10.1%.[7] Obesity is one of the most important risk factors for developing diabetes. When both conditions are considered in terms of complications, loss of workforce, and the effort and financial burdens required for disease management, they constitute a very serious disease burden.

For this reason, studies and initiatives aimed at preventing both obesity and diabetes have gained importance in recent years. The exact causes of this increase in obesity and diabetes are yet to be established. Key factors for obesity and diabetes include excess calorie intake and a sedentary lifestyle. However, there are accumulated findings about the role of nontraditional risk factors such as micronutrients, environmental chemicals, and gut microbiome in these conditions.

The body's endocrine system regulates weight, growth, and metabolic processes by generating various growth factors and hormones that are strictly integrated. Hormones regulate signaling pathways in the pancreas, liver, muscles, gastrointestinal system, adipose tissue, brain, and immune system, affecting the content and number of adipocytes, satiety, and appetite.[8-10] This review focuses on endocrine-disrupting chemicals (EDCs) and particularly their effects on obesity and T2DM in the light of the current literature.

Overview of Endocrine-Disrupting Chemicals

The US Environmental Protection Agency has described EDCs as "an exogenous substance or mixture that alters the functioning of the endocrine system, resulting in adverse health effects."[11] The Endocrine Society made a similar definition in 2009.[12] It is obvious that recent developments and advancements in chemistry have radically affected our daily life, and studies that focus on the role of environmental chemicals in obesity and diabetes has also increased. Initial data on the link between EDCs and obesity emerged based on secondary outcome results. Subsequently, studies examining the relationship between EDC obesity and diabetes as a primary outcome have gradually increased. In 2011, a report published by the US National Institute of Environmental Health Sciences about the existing literature indicated that exposure to various environmental chemicals may play a role in the epidemics of obesity and diabetes.[13]

Common EDCs are shown in Table 1. Lipophilic EDCs can enter the body mostly through food ingestion or other contact methods. They have the property of accumulating by being stored in the adipose tissue for a long time. On the other hand, nonlipophilic EDCs such as polyfluoroalkyl substances (PFASs) and perfluoroalkyl are transported by albumin and deposited in the liver. The PFASs accumulate in the food chains, and their half-lives can be long. These EDCs accumulating in the human liver are also known as persistent organic pollutants (POPs).

Table 1. Common Endocrine-Disrupting Chemicals

Lipophilic	Nonlipophilic
Polychlorinated biphenyls	Perfluoroalkyl substances
Dioxins	Polyfluoroalkyl substances
Organochlorine pesticides	
Brominated flame retardants	

On the other hand, not all EDCs accumulate and are stored in the human body. For instance, Bisphenol A (BPA), a plasticizer, has a short half-life in humans. Still, its detectable levels can be encountered, particularly in people in industrialized countries, due to daily exposure. Another huge group of EDCs are phthalates that have a short life. These chemicals are used as plasticizers and solvents.

EDCs are widely utilized daily and can be found abundantly in the environment. Exposure to EDCs early in life and during developmental stages has been reported to increase the risk of occurrence of several chronic diseases, including obesity and diabetes. These substances lead to weight gain through lipid metabolism alteration to promote lipid accumulation and adipogenesis.[14] This has been demonstrated to occur through an increase in the size and number of adipocytes and fat storage per cell and alteration of endocrine pathways responsible for hormones that play a role in the regulation of basal metabolic rate, insulin sensitivity, energy balance, appetite, satiety, and several organs and tissues with lipid metabolism such as liver, pancreas, liver, gastrointestinal tract, brain, and adipose tissue.[14]

It has been shown that only low EDC levels are needed to change development as the protective mechanism in adults because the ability to repair DNA, a competent immune system, liver metabolism, the brain–blood barrier, and a normal metabolic rate may not yet be developed in the early period of life.[15]

Endocrine Disruption, the Obesogen, and Diabetogenic Hypotheses

In 2002, a hypothesis was proposed linking the increased new industrial chemicals and the beginning of obesity endemic.[16] When excess lipid is stored, adipose tissue expands to accommodate it through hypertrophy of existing adipocytes and differentiation of preadipocytes. Developing a dysfunctional adipose tissue contributes to obesity and obesity-related metabolic complications. Grün et al's[17] 2006 study, which coined the term "obesogens," defined them as "xenobiotic chemicals that can disrupt normal developmental and homeostatic controls on adipogenesis and/or energy balance." These and other related studies gave rise to the "obesogen hypothesis," which proposes that prenatal or early life exposure to certain EBCs predisposes some individuals to gain fat mass and become obese. The obesogen hypothesis suggests that environmental EDCs, called obesogens, may cause obesity by affecting metabolic control points, appetite and satiety center regulation, and adipocyte differentiation.[18,19] (Figure 1).

After postulating the environmental obesogen hypothesis, the effects of EDCs began attracting more interest from scientific society. These effects generally start in early developmental stages, leading to obesity later in life. Numerous environmental obesogens are EDCs that interfere with normal endocrine metabolism, the development

MAIN POINTS

- Obesity and diabetes are increasing worldwide, and they maintain their importance as global public health problems.
- The increase in obesity and related diabetes is attributed to genetic and environmental factors.
- Data on the role of endocrine-disrupting chemicals in the pathogenesis of obesity and diabetes are increasing.
- Apart from epidemiological studies, in vitro studies, experimental studies, and animal studies confirm the role of endocrine-disrupting chemicals in developing these clinical entities.

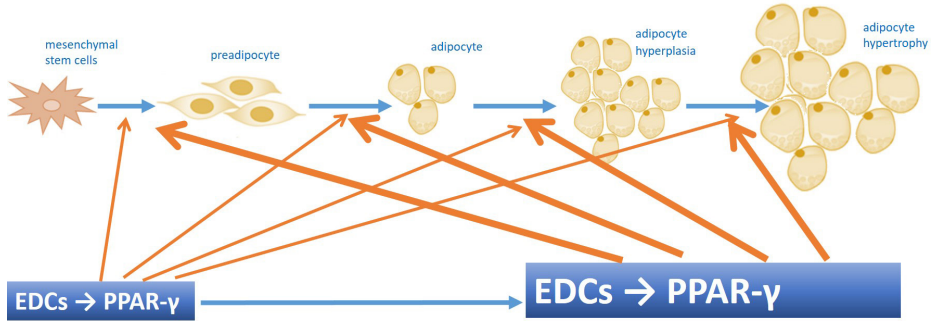

Figure 1. Effects typically demonstrated with tributyltin EDCs are suggested to accelerate adipogenesis through the key role of PPAR-γ. Endocrine-disrupting chemicals increase adipocyte differentiation, hyperplasia, and hypertrophy in adipogenesis. In addition, the accumulation of EDCs increases more in increased adipocytes, and increased levels of EDCs contribute to the formation of obesity with this vicious circle. EDCs, endocrine-disrupting chemicals; PPAR, peroxisome proliferator-activated receptor γ.

of fatty tissue, and the balance between appetite, weight gain, and energy.[20]

This hypothesis, supported by experimental studies, proposed that exposure to synthetic chemicals in the prenatal period or early life may predispose people exposed to these EDCs to increased excess weight and fat mass. Animal experimental studies have reported that several environmental pollutants promote adipogenesis and weight gain, suggesting that these synthetic chemicals are involved in the pathogenesis of obesity.

The development of T2DM is normally associated with a strong genetic predisposition and environmental factors such as obesity, aging, and lack of physical activity. Obesity triggers insulin resistance through adipokines circulating in the blood and released from fat cells. Some EDCs have been proven to induce insulin resistance in cellular and animal models, leading to the "diabetogenic hypothesis" (much in line with the "obesogen hypothesis") (Figure 2).

The diabetogenic hypothesis proposes that "regardless of its obesogenic potential and its accumulation in adipocytes, any EDC circulating in plasma capable of producing insulin resistance can be considered a risk factor for the metabolic syndrome and type 2 diabetes."[21] The diabetogenic effect of EDCs may explain, at least in part, the concept of being metabolically obese despite normal body weight. This phenotype is particularly prevalent in Asia, with a discrepancy between obesity and T2DM rates.[22]

Sources of Endocrine-Disrupting Chemicals

While some EDCs, such as plant phytoestrogens, are naturally found in vegetation and other sources, most synthetic chemicals are waste, environmental pollution, and some manufactured products. They are released into the environment as a result of interactions. Unfortunately, today, humans are exposed to these chemicals in both outdoor and indoor environments. Their intake may be in the form of dermal absorption, inhalation, or oral. Some more commonly used EDCs are shown in Table 2.

Tributyltin (TBT) is one of the environmental contaminants applied to the hulls of ships. It has been shown to masculinize female fish.[23] It can interfere with aromatase, which has a role in converting testosterone into estrogen.[24] Diethylstilbestrol (DES) is one of the synthetic nonsteroidal substances given to millions of women to prevent the

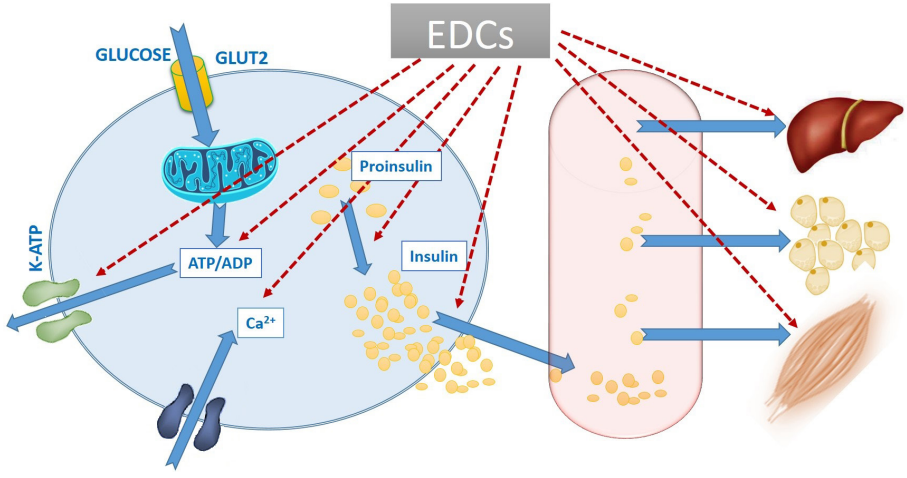

Figure 2. According to the diabetogen hypothesis, some EDCs such as BPA and dioxins cause beta cell failure by affecting the synthesis and secretion of insulin in beta cells through different pathways. Other than that, some EDCs have been suggested to cause insulin resistance in peripheral tissues independently of the increased adipokines associated with obesity. BPA, bisphenol A; EDCs, endocrine-disrupting chemicals.

Table 2. Environmental Chemicals Associated with Obesogenic Properties

Chemical	Source/Commercial Use	Potential Mechanism
Polycyclic aromatic hydrocarbons		Inflammation
Tributyltin	Fungicides, dyes, and components of polyvinyl chlorides	Peroxisome proliferator-activated receptor γ activation and fat cell differentiation ↑
Bisphenol A	Plastics and epoxy resins	Estrogenic effect, inhibition of proliferation of neural progenitor cells
Flame retardants	Chemicals applied to furniture and electronics	Adipogenesis rate, glucose intolerance ↑
Polybrominated biphenyls	Coolants, plasticizers and flame retardants	Bioaccumulation in fat cells
Phthalates	Plasticizers, adhesives, and personal care products	Adipocyte differentiation rate
Perfluorooctanoic acid Perfluorooctanoate and perfluorooctane sulfonate	Components of lubricants, nonstick coatings, and stain-resistant compounds	Serum insulin and leptin levels ↑

risk of miscarriage before its prescription has been stopped.[25] It has also been utilized to enhance fertility, especially in farm animals consumed as food. Persistent organic pollutants that are found in the environment are among stable compounds made by humans. Many POPs are lipophilic; they are deposited in fatty tissues, passing food chains in the fat found in animals. Dichlorodiphenyltrichloroethan e and dichlorodiphenyldichloroethylene, which is its breakdown product, accumulate in the adipose tissue of humans and have been proven to be among EDCs.[19] Phthalates and BPA are mainly used to produce plastic materials. Bisphenol A is used for its cross-linking feature in numerous products, including epoxy resins and polycarbonate plastics, and a wide spectrum of consumer products such as water bottles, coating and food and beverage cans, lining of water pipes, and thermal paper. Bisphenol A has been reported to have EDC characteristics.[26] Phthalates are among the phthalic acid esters that increase plastic items' durability, flexibility, and transparency. Phthalates are used in various consumer products, from children's toys to paints, and have endocrine-disrupting properties.[19] Polybrominated biphenyls and polybrominated diphenyl ethers are mainly used as flame retardants. These substances are detectable in the tissues of humans, and they have EDC properties due to their interaction with thyroid function.[27]

4-Nonylphenol is a long-chain alkyl phenol used as a surfactant in domestic and industrial practice. Parabens are *p*-hydroxybenzoic acid esters primarily used as antimicrobial preservation products in pharmaceutical products, personal care products, papers, and foods. Parabens are abundantly detected in the tissues of humans and have endocrine-disrupting features. Phytoestrogens are primarily obtained from plants and taken by humans through diet. They are found in soybeans, chickpeas, lentils, and legumes. Phytoestrogens term refers to estrogen-related activity.[19]

Ten Recommendations to Minimize Exposure to Endocrine-Disrupting Chemicals

Encarnação et al[28] reported a summary of "Ten recommendations to minimize exposure to EDCs" derived from the individual experts and expert panels of the US Endocrine Society, the WHO, and the United Nations Environment Programme:

- It is preferable to opt for fresh food instead of processed and canned foods.
- It is preferable to opt for added chemicals-free food.
- Food in plastic containers should not be heated in a microwave oven. Plastic containers can be replaced by glass or ceramic ones.
- The consumption of fat dairy or meat products should be reduced.
- Products such as makeup, perfume, and skin care should be free of phthalates, parabens, triclosan, and other chemicals.
- It is preferable to opt for ecological household cleaning products.
- Flame retardant-treated furniture should be avoided.
- Indoor environments should be ventilated regularly.
- Alternatives to plastic toys are preferred.

Obesogenic Endocrine-Disrupting Chemicals and Their Mechanism of Action

Obesogens are crucial in obesity via various pathways that induce lipid accumulation and adipogenesis. In general, obesogen exposure, especially during the prenatal period, causes an increase in the number of adipocytes. Peroxisome proliferator-activated receptor gamma (PPAR-γ) function is the main mechanism involved in adipogenesis (Figure 1). Tributyltin has been demonstrated to bind heterodimer retinoid X receptor (RXR)–PPAR-γ and induce adipogenesis.[20] Many other studies have shown that the conversion of 3T3-L1 fibroblasts is accelerated when incubated with insulin.[29-31] Mono-(2-ethylhexyl) phthalate has been shown to play a role in the activation of PRAR-γ, promoting adipogenesis by activating various PRAR-γ target genes.[32] Benzyl butyl phthalate (BBP) plays a role in differentiating 3T3-L1 by metabolic disturbance and activating the adipogenic pathway. Parabens have been shown to induce adipogenesis 3T3-L1 murine cells, messenger RNA (mRNA) expression of adipocyte-specific markers, and accumulation of lipids. In addition, increasing the length of the linear alkyl chain causes an increase in the adipogenic potency of parabens.[32]

Another mechanism through which EDCs play a role in the pathogenesis of obesity is the change in food preference, appetite, and satiety (Figure 3). Among EDCs, BPA may show its action by permanently altering the neurobiology of metabolic homeostasis. It has been reported in humans that, after adjusting for gender, height, lean mass, fat mass, smoking, and alcohol, BPA was associated negatively with ghrelin and positively with leptin and adiponectin.[33] In the existence of BPA, mRNA levels of interleukin 6 (IL-6), interferon γ, and leptin are significantly increased.[34] Both leptin and ghrelin are released by adipose tissue in humans and regulate hunger, and while leptin inhibits hunger, ghrelin stimulates it. Another hypothesis

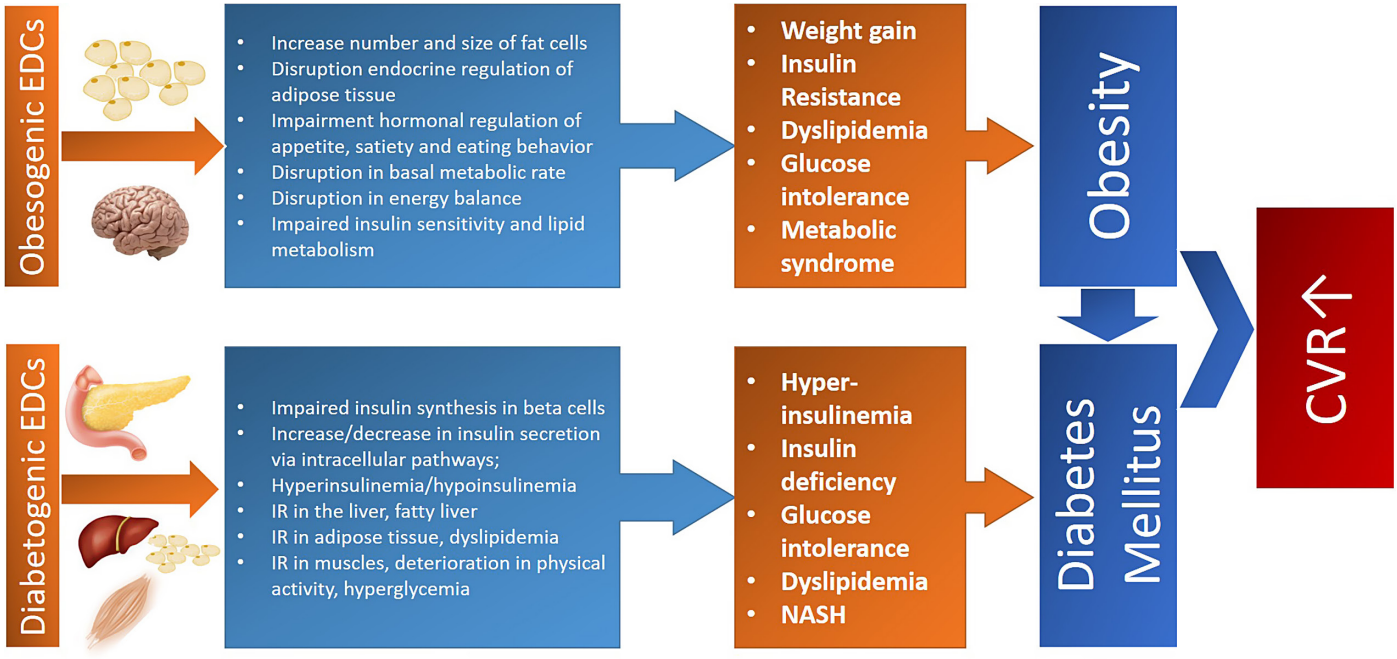

Figure 3. Interactions of EDCs in obesity, diabetes, and metabolic syndrome. While obesogen EDCs increase the risk of obesity and metabolic syndrome with many different effects, some diabetic EDCs cause beta cell dysfunction and/or peripheral insulin resistance other than obesity. CVR, cardiovascular risk; EDCs, endocrine-disrupting chemicals.

proposes that obesogens can promote a vicious pathological cycle. Obesogens can induce obesity onset. On the contrary, obesity is related to an increase in the quantity of adipose tissue, which can serve as a reservoir for obesogen items. Prolonged exposure to obesogens is a risk factor for developing metabolic disorders.

Furthermore, obesogens can have local toxicity. For instance, xenobiotics have been shown to produce fatty acid conjugates at the adipose tissue level.[35] Conjugate has the aim of eliminating toxic agents from the body. Finally, although adipose tissue could act as a reservoir, adipose tissues could not have the same ability to accumulate obesogens. For example, women are significantly different than men in terms of subcutaneous fat deposition and the endocrine function of adipocytes. The most commonly studied EDCs (obesogens) are discussed below.

Tributyltin

Tributyltin has been the first identified obesogen and is currently the most commonly studied. Tributyltin binds to and activates PPAR-γ and RXR to promote adipocyte commitment and differentiation.[36] In vivo studies have shown that TBT exposure caused the differentiation of murine 3T3-L1 adipocytes into adipocytes by activating PPAR-γ and RXR.[14] In addition, 3T3-L1 preadipocytes that were exposed to TBT caused dysfunctional adipocytes with changed lipid metabolism and gene expression.[37]

In vivo studies have found that TBT exposure increased fat accumulation and hepatic steatosis in rodents, fish, and snails.[38-40] In one of these studies, F0 mice exposed to TBT during pregnancy produced F1 offspring with increased adipose deposit.[38] The effects of prenatal exposure to TBT can be transferred to the next generations. Other studies have shown transgenerational increases in obesity with various chemicals.[41,42] Data from these studies suggest that epigenetics was likely to mediate these effects. In another experimental study, it was determined that the impact of prenatal exposure to TBT on the size of the fat depot persisted until at least F4 generation.[43] Subsequent studies supporting this model have demonstrated that this impaired organization of chromatin is either transmitted to the future generation or, more likely, self-reconstructed by each generation itself.[44]

Based on the transgenerational effects of exposure to TBT and other obesogens, since current toxicological risk assessment tools include direct exposure to chemicals, they may need to evaluate the toxicology risk comprehensively. Therefore, a risk assessment should contain "generational toxicity" to assess the effects on the next generations.

Bisphenol A

Bisphenol A was described for the first time by Dianin as a result of condensation of acetone with 2 equivalents of phenol in 1891. Today, BPA is one of the most widely produced compounds for producing epoxy resins and plastics worldwide. It is polymerized either with diphenyl carbonate or carbonyl chloride to have polycarbonate plastics. Polycarbonate plastics are used in materials to serve and store food, including beverage bottles, storage containers, and reusable cans. Epoxy resins used in the lining of food packages and beverage cans and the protective coating are also produced with BPA. Small amounts of BPA can contaminate beverages and food stored in materials containing it. It is estimated that 99% of BPA exposure is attributable to food consumption. Studies from the United States have shown that BPA and BPA metabolites can be detected by approximately 92.6% of the population in urine samples.[45]

Furthermore, BPA has been detected in breast milk and placental amniotic fluid, suggesting that exposure to BPA starts in utero and continues after birth.[46] Because the association between BPA and its detrimental effects has been revealed with increasing evidence,

in 2011, BPA was banned in plastic infant feeding bottles used in Europe. The U.S. Food and Drug Administration prohibited using BPA-containing items produced for infants in 2012, and France has not permitted the use of food contact materials since 2015. However, there still needs to be a clear standardization regarding an acceptable limit of BPA.[47]

Endocrine-Disrupting Chemicals and Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that results from defects in insulin secretion, insulin effect, or both. The chronic hyperglycemia of DM is associated with dysfunction and insufficiency of the eyes, kidneys, nerves, heart, and blood vessels. Metabolic syndrome is a group of disorders, including obesity, hypertension, glucose intolerance, and dyslipidemia. Patients with metabolic syndrome are more likely to develop cardiovascular disease, T2DM, and other diseases such as cancer. The incidence of metabolic syndrome is increasing at warning levels. Insulin resistance underlying the disease, in the case of low insulin sensitivity, the mass and function of β-cells adapt to this new form in order to maintain glucose homeostasis and prevent the development of T2DM. Only when the capacity to produce sufficient insulin is impaired, T2DM develops.[48]

Insulin resistance develops as a response to environmental factors. For example, a sedentary lifestyle and excess calorie and fat intake in the diet may cause obesity, a major factor in the occurrence of T2DM. Based on the theories proposed for developing obesity-related T2DM, insulin resistance is promoted by signaling molecules either because they are released by adipose tissue or because adipocytes do not take them up. Since various EDCs induce the accumulation of insulin resistance in adipose tissue, their eventual release should be taken as an association between insulin resistance and obesity. Apart from their existence in adipose tissue, some EDCs can also be detected in blood. Studies have reported that insulin resistance may better predict metabolic risk, especially in T2DM.[49] Therefore, every EDC in the circulation in plasma can produce insulin resistance. The potential existence and accumulated adipocytes as obesogens may be taken as a risk factor for the development of T2DM and metabolic syndrome. In Figure 3, the relationships of EDCs with obesity, metabolic syndrome, and diabetes are schematized.

Experimental Evidence of Diabetogenic Pollutants

Estrogens are key regulators for the improvement of insulin resistance as well as survival and function of β-cells and glucose homeostasis through energy homeostasis, leading to the raising of a question: Could EDCs with estrogenic properties be responsible for the dramatic worldwide rise in obesity, the metabolic syndrome, and T2DM over the past 10 years?

In Vitro Experimental Studies

Studies have reported that organic pollutants could increase insulin resistance in vitro and directly impact adipocytes. For example, in an animal study, cultured mouse adipocyte 3T3-L1 exposed to organic pollutants showed impaired response to insulin and downregulation of LPIN1 and insulin-induced gene 1, which play a key role in lipid metabolism.[50] Cultured cells' exposure to phthalates led to the activation of PPAR-α and PPAR-β, fatty acid oxidation, and strong adipose differentiation. Although the results are controversial, some dioxins have been shown to disrupt glucose uptake by adipose tissue and the pancreas in addition to the secretion of insulin.

BPA is one of the highest-volume chemicals produced worldwide. BPA is today used to produce production epoxy resins and polycarbonate plastics. It is markedly detected in food storage containers, bottles, and dental seals. This explains the reason for the detection of BPA in urine and serum.[51] Most concerns related to BPA include its effects on development and reproductive health. However, it was shown to induce a rapid glucose-induced Ca^{2+} signal that is a key messenger playing a crucial role in insulin secretion. On the other hand, human adipocytes have also been demonstrated to be targets of BPA, causing an insulin resistance state that could lead to T2DM when combined with a sedentary lifestyle, excess calorie intake, and genetic predisposition.[52]

In Vivo Animal Studies

Various EDCs have been demonstrated to cause biological effects that change glucose homeostasis following acute or chronic exposure in rats and mice. Acute exposure of male mice to BPA caused a rapid increase in the levels of plasma insulin and a decrease in the levels of plasma glucose, while chronic exposure to BPA was found to reduce insulin sensitivity and to induce hyperinsulinemia, suggesting that BPA may be considered a diabetogenic factor. Remarkably, the disruption of insulin action occurred despite an increase in the insulin content of β-cells and was particularly prominent when mice were exposed to BPA orally or by subcutaneous injection.[53] BPA functions via several pathways that independently lead to increased insulin synthesis while promoting peripheral insulin resistance in adipose tissue. Chronic exposure to BPA resulted in changes in whole-body energy homeostasis through a direct effect of BPA on the CNS, leading to lower energy intake and expenditure.

Perinatal Exposure

Experimental animal studies have reported that changes in nutrition during pregnancy can directly influence the programming of metabolically active tissues, promoting T2DM in the next generation.[54] Besides nutritional changes, in animal models, exposure to EDCs could also change glucose homeostasis in the mothers and infants when they become adults. Prenatal exposure to DES led to a considerably decreased body weight during treatment and then led to a significant weight gain associated with the percentage of body fat following 2 months of age. The increase in body weight continued throughout adulthood. Therefore, these DES-treated mice also showed higher levels of IL-6, leptin, and adiponectin and changed glucose levels.[55] However, the reported results of experiments on perinatal exposure to EDCs are conflicting, and further studies are needed on this topic.

Epidemiological Research

Some studies have reported an association between diabetes and high levels of POPs. The authors showed that 6 different POPs were associated with T2DM based on the National Health and Nutrition Examination Survey database. Subsequently, more than 40 published cross-sectional studies have reported an association between the levels of EDCs and diabetes in numerous countries. However, prospective studies on this topic are warranted because of the likelihood of bias with cross-sectional studies. The relationship between EDCs and diabetes was evaluated in terms of epidemiological studies with the US National Toxicology Program workshop conducted by experts in 2013. Although it was stated in this study that a meta-analysis could not be performed due to the heterogeneity of existing epidemiological studies, it was concluded that the general evidence was

sufficient to show the relationship between organochlorine POPs and diabetes. Data between perfluoroalkyl acids and brominated nonorganochloroquine POPs were found to be lower. A review of 4 studies found a strong relationship between perfluorononanoic acid and diabetes.[56,57]

Prospective evidence exists between exposure to organochlorine pesticides and polychlorinated biphenyls and incident T2DM. Furthermore, evidence exists from cross-sectional studies for the association between organochlorine pesticides and incident diabetes.[58]

Considering many gaps related to the identification of chemicals, bioaccumulation in certain tissues, and exposure to low concentrations and complex mixtures, exposure to EDCs should be avoided, especially during several sensitive periods of human life such as fetal development, early childhood, and reproductive age. There is still much more way to go to insight details of EDCs; every passing day comes with newer information. Accumulation of evidence by animal, experimental, in vitro, and in vivo studies will be the key factor for better insight into the role of EDCs in the development of obesity and T2DM. Based on this, every single piece of evidence for scientific reports is needed to enlighten the relationships between these entities.

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