Endocrine disruptor chemicals as obesogen and diabetogen: Clinical and mechanistic evidence

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Abstract

Obesity is becoming an inevitable pandemic all over the world. The World Obesity Federation predicts in the 2022 World Obesity Atlas that one billion people worldwide, including 1 in 5 women and 1 in 7 men, will be living with obesity by 2030. Moreover, the prevalence of diabetes is increasing worldwide, and diabetes is becoming more of a public health problem. Increased insulin resistance due to obesity and deficiency in insulin secretion are the two main causes of type 2 diabetes mellitus (T2DM). An exogenous chemical or mixture of chemicals that interferes with any aspect of hormone action was defined as endocrine-disrupting chemicals (EDCs). Bisphenol A (BPA), the first known EDC, was synthesized and was considered to be estrogenic. Global production of BPA has increased progressively from 5 to 8 million tons (MT) between 2010 and 2016. Furthermore, researchers estimated that the production should reach 10.2 MT by 2022. The human population is exposed to EDCs in daily life in such forms as pesticides/herbicides, industrial and household products, plastics, detergents, and personal care products. The term obesogen was used for chemicals that promote weight gain and obesity by increasing the number of adipocytes and fat storage in existing adipocytes, changing the energy balance, and finally regulating appetite and satiety. Besides the obesogenic effect, EDCs can cause T2DM through alteration in β cell function and morphology and insulin resistance. In this review, we provide clinical and mechanistic evidence regarding EDCs as obesogen and diabetogen. However, those studies are not enough methodologically to indicate causality. In this respect, randomized clinical trials are needed to investigate the association between obesogen, diabetogen and the related metabolic clinical picture.

Key Words: Endocrine disruptors; Adipogenesis; Obesity; Diabetes mellitus

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Core Tip: An exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action was defined as Endocrine-Disrupting Chemicals (EDCs). Obesogens can promote obesity by increasing the number of adipocytes and fat storage in existing adipocytes, changing the calories burned at rest, changing the energy balance, and finally regulating satiety. Besides the obesogenic effect, EDCs can cause type 2 diabetes mellitus through alteration in ß cell function and morphology and insulin resistance. In this review, we provide clinical and mechanistic evidence regarding EDCs as obesogen and diabetogen.

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INTRODUCTION

Obesity has become a “preventable” pandemic affecting people of all ages around the world. Globally, obesity has nearly tripled since 1975. In 2016, 39% of adults (more than 1.9 billion) aged 18 and over were overweight and 13% (more than 650 million) were obese[1]. The World Obesity Federation predicts in the 2022 World Obesity Atlas that one billion people worldwide, including 1 in 5 women and 1 in 7 men, will be living with obesity by 2030[2]. The International Classification of Disease defines obesity as a chronic, recurrent, and multifactorial disease[3]. It is also a significant risk factor for several other non-communicable diseases (NCDs), such as metabolic diseases e.g., type 2 diabetes mellitus (T2DM) and fatty liver, cardiovascular diseases (such as hypertension, myocardial infarction, and stroke), and some malignancies (including breast, ovarian, prostate, liver, kidney, and colorectal cancers)[4]. Obesity affects the mind and body in many ways, including hunger, satiety, metabolism, hormone balance, and body weight. These changes can remain the same for many years, even if the weight is lost. In addition, obesity is a disease that recurs frequently. This means that individuals are treated without changing the obesogenic environment and other underlying causes, and then individuals are re-exposed to the same environment[2].

Diabetes is a progressive chronic disease that occurs when the pancreas cannot produce enough insulin, or the body cannot use the produced insulin effectively. The prevalence of diabetes is increasing worldwide, and diabetes is becoming more of a public health problem.

In 2021, an estimated 537 million adults worldwide were living with diabetes[5], up from 108 million in 1980[6]. The global prevalence of diabetes has more than doubled since 1980, from 4.7% to 10.5%. In the 10th edition of the Diabetes Atlas published by the International Diabetes Federation, it is estimated that 643 million adults will be living with diabetes by 2030, and 783 million adults by 2045[5]. In addition, total health expenditures related to diabetes are projected to be $966 billion, $1028 billion, and $1054 billion in those years, respectively. Another feature of these expenditures is that the prevalence of diabetes has been increasing rapidly over the past three decades, with this increase being even faster in low- and middle-income countries.

Diabetes is treatable and its consequences can be avoided or prevented by diet, physical activity, medications, and regular check-ups. However, diabetes is still a major cause of blindness, kidney failure, lower limb amputation, and many other conditions that affect the quality of life in the long term[7].

ENDOCRINE DISRUPTORS

Endocrine disruptors were defined as, “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action”, in The Endocrine Society’s Second Scientific Statement on endocrine-disrupting chemicals (EDCs)[8]. The history of EDCs goes back a long time. The first known EDC, Bisphenol A (BPA), was synthesized in 1891 and was considered to be estrogenic in 1936[9]. However, we must keep in mind that by definition there can be hundreds of other EDCs.

Persistent organic pollutants

Persistent organic pollutants (POPs) are a group of chemicals that include pesticides (DDT, HCB) and industrial chemicals, for instance, polychlorinated biphenols (PCBs) (Figure 1). POPs bioaccumulate in tissues and amplify up the food chain[10]. POPs persist in the environment for long periods because they are chemically resistant to environmental degradation. They can accumulate and pass from one species to the next through the food chain[11]. Three kinds of POPs named chlorinated, hydrophobic, and brominated accumulate predominantly in adipose-rich tissues[12].
In addition, adipose tissue plays an important role in POP’s storage and toxicokinetics. Adipose tissue stores these chemicals and acts as a buffer. On the other hand, it is a source of constant internal exposure\cite{13}. Although the use of many POPs, especially PCBs, HCB and DDT, is prohibited in most countries, exposure still exists due to their persistence in the environment\cite{14-16}.

**Heavy metals**

Heavy metals are directly related to many cancers. Besides this, two heavy metals, arsenic, and cadmium, are also classified as EDC.

**Cadmium**

Mining, metallurgy, electroplating, paints, combustion fumes, and overuse of fertilizers and pesticides are the main sources of cadmium contamination\cite{17}. As it is more mobile and soluble compared to other metals, it is quickly absorbed by plants and accumulated in their edible parts\cite{18,19}. Cadmium began to attract attention as an EDC with the discovery of the ability of cadmium and other heavy metals to activate the estrogen receptor\cite{20}. Initially, it was discovered that cadmium binds with high affinity to purified ER\(\alpha\) cells and activates them\cite{21}.

**Arsenic**

Inorganic arsenic (iAs) is found naturally in soil and in ground and surface water. This exposure can vary by location and diet. So, exposure to detrimental levels can be widespread\cite{22}. Although multiple mechanisms, including DNA damage and oxidative stress, influence toxicity, there is also some evidence pointing to the interaction of arsenic with steroid receptors\cite{23-25}. In a broader context, these studies provide new evidence that iAs exposure targets many receptors and have many effects that can be considered as an EDC\cite{26,27}.

**Other “non-persistent” phenolic compounds**

Non-persistent endocrine disrupting chemicals refers to a wide variety of chemical compounds used in industrial applications whose main characteristic is a shorter half-life and lower lipid solubility. Nevertheless, with constant exposure, they are continually present in biological samples of the general population\cite{28}. They are commonly encountered in plastics, medical devices, cosmetics, and detergents\cite{29}. Although there are members of this group such as paraben triclosan and phthalates, the most well-known member is BPA.

**BPA**

In 1891, the first known EDC, BPA, was synthesized and was considered to be estrogenic in 1936 (Figure 1)\cite{9}. Global production of BPA has increased progressively from 5 to 8 million tons (MT) between 2010 and 2016 and is estimated to reach 10.2 MT by 2022\cite{30,31}. Most of the BPA produced is used to produce polycarbonates and epoxy resins\cite{32,33}. However, it is readily found in air\cite{34}, soil
these compounds may also affect hormonal activities. The European Union has been phasing out pentabromodiphenyl ethers in the United States and their prohibition in the European Union has led to a reduction in exposure to these chemicals. It has also been noted that TSC reduces the total level of T3 in plasma, milk, urine, brain, liver, and adipose tissue. Plasma, milk, urine, brain, liver, and adipose tissue. Polybrominated diphenyl ethers (PBDEs), commonly used in upholstered furniture, car seats, cushions, carpet padding and clothing, are mainly used as flame retardants. Polybrominated diphenyl ethers are known to be released into the blood, especially during weight loss. Fatty fish, as well as shellfish, have a high solubility in fat. Phthalates can also be considered as exposure routes. Triclosan is an extensively used antibacterial agent generally found in antibacterial soaps, toothpaste, oral rinses, toothbrushes, cutting boards, detergents, and plastics in furniture, toys, and sporting goods. It has been noted that phthalates can accumulate in fatty foods such as mayonnaise, dairy products, fatty meat and fish, as well as shellfish, as they have a high solubility in fat. High phthalate exposure has been linked with increased threat of obesity and infertility, increased body mass index (BMI) and waist circumference, insulin resistance, and a change in thyroid hormones. Although this and many similar studies consider TCS to be a substance that threatens human health, another group has not been able to determine a correlation that would require TCS to be classified as EDC. Polybrominated diphenyl ethers are poorly bio-degradable and highly bioaccumulative in the food chain. Tordjman et al. notes that phthalates can accumulate in fatty foods such as mayonnaise, dairy products, fatty meat and fish, as well as shellfish, as they have a high solubility in fat. High phthalate exposure has been linked with increased threat of obesity and infertility, increased body mass index (BMI) and waist circumference, insulin resistance, and a change in thyroid hormones. Although many of these studies have found an association between phthalates and obesity, the correlation has not been confirmed by all studies. On the contrary, a few studies have reported a negative correlation. The correlation between phthalate exposure and obesity is, obviously controversial. It should be emphasized that most studies are cross-sectional. Therefore, large prospective studies are needed that would confirm or invalidate the existence of this association.

BPA substitutes

As mentioned in the forthcoming sections, when various countries restricted or banned the use of BPA, BPA substitutes [e.g., bisphenol S (BPS) and bisphenol F (BPF) and bisphenol AF (BPAF)] began to be used instead of BPA (Figure 1). However, some later studies have revealed that these substitutes also present hormonal activity. And these analogues are increasingly being detected in human urine. The products labeled as “BPA free” use BPA analogues. This situation also enlarges the risk of exposure to these chemicals in the intrauterine period or in infancy.

Phthalates

Phthalates are a group of chemicals used as liquid plasticizers to increase the elasticity of plastic products. Medical devices, including parenteral feeding tubes, personal care products such as nail polish and perfume, food packaging, and toys contain various phthalates. Unfortunately, phthalates are poorly bio-degradable and highly bioaccumulative in the food chain. It was found that the highest exposure comes from foods that absorb the compound from their packaging or during the production process. Tordjman et al. notes that phthalates can accumulate in fatty foods such as mayonnaise, dairy products, fatty meat and fish, as well as shellfish, as they have a high solubility in fat. High phthalate exposure has been linked with increased threat of obesity and infertility, increased body mass index (BMI) and waist circumference, insulin resistance, and a change in thyroid hormones. Many epidemiological studies have been conducted, especially on body weight and obesity. Although many of these studies have found an association between phthalates, obesity, and weight gain, some studies have not found a significant association. On the contrary, a few studies have reported a negative correlation. The correlation between phthalate exposure and obesity is, obviously controversial. It should be emphasized that most studies are cross-sectional. Therefore, large prospective studies are needed that would confirm or invalidate the existence of this association.

Triclosan

Triclosan is an extensively used antibacterial agent generally found in antibacterial soaps, toothpaste, oral rinses, toothbrushes, cutting boards, detergents, and plastics in furniture, toys, and sporting goods. Since Triclosan (TCS) can be mixed into nature from domestic wastewater, water and food can also be considered as exposure routes. After ingestion, TCS can be noticed in the blood, plasma, milk, urine, brain, liver, and adipose tissue. In the Weatherly and Gosse's study, it was noted that TCS reduces the total level of T3, increases the risk of spontaneous abortion, reduces fertility, and lowers BMI. Although this and many similar studies consider TCS to be a substance that threatens human health, another group has not been able to determine a correlation that would require TCS to be classified as EDC.

Polybrominated diphenyl ethers

Polybrominated diphenyl ethers (PBDEs), commonly used in upholstered furniture, car seats, cushions, carpet padding and clothing, are mainly used as flame retardants. Humans may be exposed to polybrominated diphenyl ethers through consumption of foods such as fatty fish, consumption of contaminated water or soil, and inhalation of air containing polybrominated diphenyl ethers. Due to their highly lipophilic structure, PBDEs tend to accumulate in adipose tissue and these chemicals can be released into the blood, especially during weight loss. Many studies show that PBDEs are associated with metabolic syndrome and obesity. In addition, insulin resistance in obese individuals has also been associated with the accumulation of PBDEs in adipose tissue. After the phasing out of pentabromodiphenyl ethers in the United States and their prohibition in the European Union, alternative PBDEs were used in new furniture. However, it is suspected that these compounds may also affect hormonal activities.
**OBESOGEN HYPOTHESIS**

The term obesogen was coined for chemicals that promote weight gain and obesity. Obesogens can promote obesity by increasing the number of adipocytes and fat storage in existing adipocytes, changing the calories burned at rest, changing the energy balance, and finally regulating appetite and satiety. In other words, obesogens can cause the development of obesity in a person's later life by modifying the "set point". It can be said that the main mechanism of the effects of obesogen exposure in later life during development is epigenetic changes. The individual's unique epigenetic system determines how the individual's hormonal regulatory system works. These decisions are, of course, directly related to hormonal processes such as appetite and weight gain. Epigenetic regulation of gene expression involves methylation of the CpG islands\[^74\] , probably in the gene promoter region, leading to repression of gene expression, and covalent modification of the tails of histone proteins that package DNA\[^75\]  .

These modifications that occur during the development of the tissue are involved in the differentiation of the tissue during cell division, especially during mitosis. Although generally stable, environmental chemicals and changes in diet can lead to changes in the epigenetic marks, especially during development\[^8\],\[^75\] . In conclusion, the obesity hypothesis makes two important points. The first is that the susceptibility to obesity begins during the development of the individual, both intrauterine and in the first years of life. The second is that EDCs that alter developmental programming, *i.e.*, the "set point", predispose one to weight gain and obesity later in life\[^14\] . Another important conclusion is that habitual causes such as diet and exercise are not the only root of obesity, as we have seen in studies of obesity. It has also been shown that genes and environment (especially in the intrauterine and subsequent postpartum years), and the interactions between them are quite important.

In his article, Heindel *et al*\[^14\] explains the importance of the obesogen hypothesis for the treatment of obesity and states that the obesogen hypothesis has shifted attention from genetics to the environment as a major cause of obesity. The focus of discussion has shifted from mostly unsuccessful treatment to prevention, and the timing of predisposition to obesity has shifted from adulthood to the developmental age. Therefore, it was helpful for us to focus on a different age group and the protection of that age group. Furthermore, this hypothesis gives us hope that the pandemic of obesity can be prevented by arguing that obesity is a disease acquired by environmental exposure, and therefore preventable, rather than a genetic inheritance.

**DIABETOGEN HYPOTHESIS**

The diabetogen hypothesis is similar and parallel to the obesity hypothesis. The main reason for this hypothesis is that some EDCs, especially POPs, predispose to T2DM independently of obesity\[^13\] . Many studies have shown that POPs and others, increases peripheral insulin resistance and alters insulin production and secretion\[^13\],\[^76\] . The diabetogenic effect of EDCs, at least partially, explains why some people are metabolically obese despite being of normal weight\[^77\] .

**CLINICAL AND MECHANISTIC EVIDENCE**

Due to ethical issues, it is quite difficult to design a double-blind trial on EDCs. For this reason, the studies can be divided into these four groups: Embryological analysis of EDC exposure (mainly in rodent models), studies of the mechanism of exposure (gene expression and epigenetic changes in cell and tissue cultures), studies examining the association between EDC and diseases (most of which are epidemiological studies), and reports of occupational or acute exposure to one or more chemicals known to be EDCs.

BPA is mainly used to make epoxy resins and polycarbonate. It is by far one of the most commonly exposed EDCs because of its widespread use and, particularly, its long-term use in sectors such as toys and food packaging. As a result, epidemiological studies have concentrated on BPA and phthalates in general. Only the most up-to-date studies and studies with divergent results are included here, because the study models are generally similar and there are no obvious differences between the outcomes.

**Clinical evidence for BPA as an obesogen**

Various recent studies have found a correlation between BPA and obesity. BPA urine levels were strongly correlated with BMI and waist circumference in 296 women of reproductive age\[^78\] . In the study conducted by Choi *et al*\[^79\] , it measured the prenatal BPA exposures of 59 children. They classified those remaining above the 80th percentile as high exposure and others as low exposure. The study examined 594 obesity-associated CpG sites from children's methylation profiles. As a result, high methylation in the insulin-like growth factor 2 receptor region was detected in the 2-year-old high exposure group. This study has strengthened the notion that BPA exposure affects humans through the mechanism of methylation\[^79\] .
Extensive studies published in recent years clearly reveal the relationship between BPA and obesity. A study of 888 middle-aged and elderly Chinese conducted in China found a positive association between urinary BPA concentration and central obesity[80]. A study by the Canadian Health Measures Survey found a positive correlation between urinary BPA levels and BMI-defined obesity. However, no relationship was found between waist circumference and urinary BPA using the standard cut-offs. In addition, for each natural logarithmic unit increase in urinary BPA concentration, an increase in the BMI of 0.33 kg/m² and a waist circumference of 1 cm was observed[81]. The National Health and Nutrition Examination Survey (NHANES) studies in 2003-04 and 2005-06 found a significant positive association with obesity when comparing the highest and lowest quartiles of urinary BPA[82]. This study was adjusted for traditional risk factors. Likewise, the Korean national health study used the Covariate-Adjusted Standardization (CAS) Method to prevent factors such as age, gender, education, urinary creatinine, income, alcohol, and smoking from affecting the study. After using the CAS method, a positive relationship with obesity was determined by comparing the highest and lowest quartiles of urinary BPA[83]. Wu et al[84] showed in their meta-analysis that there was a positive correlation between BPA exposure and obesity. According to the dose-response analysis, an increase of 1 ng/mL BPA causes an increase of 11% risk in obesity.

**Clinical evidence for BPA as a diabetogen**

Evidence from individual epidemiological studies is usually inconsistent in regards to the association of BPA exposure and T2DM, so it is unclear whether exposure to BPA is a risk factor for the development of T2DM. Population ethnicity, lifestyle, eating habits, use of BPA-containing products, different sample size, and differences in T2DM criteria are the factors that may account for the inconsistent findings[85]. One of the meta-analysis (n = 41,320) included 16 epidemiological studies (12 cross-sectional, 2 case-control, 1 prospective) that showed a positive association between BPA levels and T2DM risk with a pooled OR of 1.28 (95%CI 1.14-1.44)[86]. Another meta-analysis, including 41 cross-sectional and 8 prospective studies from ethnically diverse populations, evaluated the association of dioxin, PCB, chlorinated pesticide, BPA and phthalate with T2DM, and related metabolic features. Serum concentrations of dioxins, PCBs, and chlorinated pesticides were significantly associated with T2DM risk. Urinary concentrations of BPA and phthalates were also associated with T2DM risk with pooled RR of 1.45 (95%CI 1.13-1.87) and 1.48 (95%CI 0.98-2.25), respectively[87].

On the other hand, few studies have shown that BPA can trigger diabetes independent of obesity. Silver et al[88] analyzed the NHANES results and Tai et al[89] analyzed the CMHS results and found a positive correlation between BPA and glycated haemoglobin. Another study reversed the experimental mechanism. When the study compared urinary BPA in individuals with impaired glucose tolerance (IGT) and normal glucose tolerance (NGT), the results showed that urinary BPA was higher in individuals with IGT[90]. When a similar study was conducted with participants with T2DM and NGT, it was found that participants with T2DM had higher urinary BPA[91]. In addition, BPA has also been found to be positively associated with high blood insulin resistance[76,87], prediabetes risk[92], and T2DM[93,94].

**Clinical evidence for BPA substitutes**

Many countries have regulated BPA. BPA was banned from bottles in Canada in 2008, Denmark in 2009, France in 2010, and the European Union and Turkey in 2011[95-97]. In addition, Sweden and France banned the use of BPA in food products designed for children under the age of 3 in 2011 and 2013, respectively[98]. Such regulations have led to the development of substitutes such as BPS and BPF.

However, as previously mentioned, the hormonal activities of BPA substitutes (generally BPS, BPF, BPAF) were also of the same magnitude and similar effect as BPA in the *in vivo* and *in vitro* studies[46]. A NHANES analysis showed the positive association between BPS and obesity, particularly in children and adolescents[98,99]. When Duan et al[100] examined BPA equivalents BPAF and BPS, they reported a positive correlation with T2DM.

A group analyzed the NHANES 2003-2014 results. They state that the urinary BPA concentration has decreased over the years in a trend analysis. Bans on BPA since 2009 may have contributed to this. As a result, the researchers indicated that the positive relationship between obesity and urinary BPA diminished between 2009 and 2014[101]. Since then however, obesity has been on the rise. It is noteworthy that the oral bioavailability of EDC candidate chemicals such as BPS is higher than BPA[102] and that the half-life is longer[103].

**The fundamental mechanistic principle of obesogen**

EDCs can mimic hormonal actions through the nuclear hormone receptor superfamily like steroid hormone receptors, thyroid hormone receptors, retinoid X receptors (RXR), peroxisome proliferator-activated receptors (PPAR), liver X receptors, and farnesoid X receptors[104]. The nuclear hormone receptor PPAR gamma dimerize with RXR and bind to PPAR-responsive DNA regulatory elements, which leads to the controlling of fat cell differentiation. In this way, genes responsible for adipogenesis, lipid, and glucose metabolism are controlled[105]. Dysregulation of PPARy can cause obesity and metabolic disorders. PPARy can bind to BPA, perfluorinated compounds (PFCs) and phthalates leading
 Humans are exposed to a variety of EDCs with obesogenic and diabetogenic effects. Those chemicals change the hormonal balance with different mechanisms of action. The exposure to obesogens can...
Figure 2 Potential effects of endocrine-disrupting chemicals on brown and beige adipogenesis. BPA: Bisphenol A.

Figure 3 Changes in the hypothalamus, adipocyte and gut microbiota caused by bisphenol A exposure in favor of obesity. BPA: Bisphenol A; LPS: Lipopolysaccharide; SCFA: Small chain fatty acid; NPY: Neuropeptide Y; AgRP: Agouti related peptide; PPAR: peroxisome proliferator-activated receptors; FABP4: Fatty acid binding protein 4; CD36: Cluster of differentiation 36.

happen during the different stages of life. In this context, perinatal exposure can be important as far as the permanent and transgenerational effects are concerned. EDCs promote adipogenesis leading to fat accumulation, which causes alteration in lipid metabolism and satiety as obesogens. EDCs have shown the potential to induce adipose tissue dysfunction not only in white adipocytes but in brown and beige fat as well. Besides an obesogenic effect, EDCs can cause T2DM through alteration in β cell function and morphology, and insulin resistance. The studies related to EDCs and obesity, and T2DM are not enough methodologically to show causality. In this respect, randomized clinical trials are needed to investigate the association between obesogen, diabetogen, and the related metabolic clinical picture. Future studies will be important to take political action and to increase the awareness of the population about the exposure to obesogen and diabetogen EDCs.
Figure 4 Summary of the effects of obesogen and diabetogen on tissues and the relationship of these effects with obesity and diabetes. T2DM: Type 2 diabetes mellitus.

FOOTNOTES

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