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REVIEW PAPER

Exposure to Endocrine-Disrupting Chemicals and Type 2 Diabetes Mellitus in Later Life

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Abstract

Type 2 diabetes mellitus (T2DM), one of the most common chronic metabolic diseases, involves a complex interaction among genetic, epigenetic, and environmental risk factors. The incidence and prevalence of T2DM are rapidly increasing globally. In recent years, increasing body of evidences from both human and animal studies have displayed an association between exposure to early unfavorable life factors such as endocrine-disrupting chemicals (EDCs) and the prevalence of T2DM in later life. The exogenous EDCs can lead to disadvantageous metabolic consequences because they interfere with the synthesis, secretion, transport, binding, action, and metabolism of endogenous hormones. EDCs also have long-term adverse effects on newborns, children, and adolescents by causing increased susceptibility to T2DM in adults. This review summarizes the most recent advances in this field, including diabetes-related EDCs (bisphenol A, phthalates, chlordane compounds, parabens, pesticides, and other diabetes-related EDCs), EDC exposure and gestational diabetes mellitus, prenatal and perinatal EDC exposures and T2DM, adult EDC exposure and T2DM, transgenerational effects of EDCs on T2DM as well as the possible diabetogenic mechanisms.

Keywords Type 2 diabetes mellitus · Epigenetics · Endocrine-disrupting chemicals · Exposure

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ART	Assisted reproductive technologies
ATP	Adenosine triphosphate
BeP	Benzylparaben
BMI	Body mass index
BPA	Bisphenol A
BPS	Bisphenol S
BuP	Butylparaben
BzP	Benzyl substituted para-hydroxybenzoic acid ester
CHL	Chlordane compound
CI	Confidence interval
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DEHP	Di-2-ethylhexyl phthalate
EDC	Endocrine-disrupting chemical
ER	Estrogen receptor
EtP	Ethylparaben
GCK	Glucokinase
GDM	Gestational diabetes mellitus
Glp1r	Glucagon-like peptide 1 receptor
GPR30	G protein-coupled receptor 30
GSIS	Glucose-stimulated insulin secretion
HCB	Hexachlorobenzene
HR	Hazard ratio
IGT	Impaired glucose tolerance
IL-6	Interleukin-6
MBzP	Monobenzyl phthalate
MCP1	Monocyte chemoattractant protein 1
MCPP	Mono-(3-carboxypropyl) phthalate
MeP	Methylparaben
MetS	Metabolic syndrome
MiBP	Mono-isobutyl phthalate

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MnBP	Mono-n-butyl phthalate
OR	Odds ratio
PCB	Polychlorinated biphenyl
PFAS	Per- and polyfluoroalkyl substances
PrP	Propylparaben
RR	Risk ratio
RXR	Retinoid X receptor
RXRα	Retinoid X receptor α
T2DM	Type 2 diabetes mellitus
TBT	Tributyltin
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
β-HCH	β-Hexachlorocyclohexane

Introduction

Type 2 diabetes mellitus (T2DM), a common chronic metabolic disease, has become a major public health problem. Chronic hyperglycemia due to impaired insulin secretion from pancreatic β-cells, hyperglucagonemia because of compensatory glucagon secretion from pancreatic α-cells, insulin resistance in peripheral target tissues, and hyperlipidemia are its main characteristics (Chamberlain et al. 2016; Chatterjee et al. 2017). Despite a lot of incredible advancements in biomedical sciences, diabetes mellitus is still an incurable life-long disease. Over the past 30 years, the prevalence of diabetes has rapidly increased in all age and gender clusters, in both rural and urban regions, or in developing and developed nations across the globe (Meo et al. 2021). It has been estimated that the global diabetes prevalence in 2019, 2030, and 2045 is 9.3% (463 million people), 10.2% (578 million), and 10.9% (700 million), respectively. It is higher in urban than in rural areas (10.8% vs. 7.2%), or in high-income than in low-income countries (10.4% vs. 4.0%). Unfortunately, half of the T2DM patients (50.1%) do not know that they are suffering from the disorder. In addition, it is also estimated that the global prevalence of impaired glucose tolerance (IGT) is 7.5% (374 million) in 2019, 8.0% (454 million) in 2030, and 8.6% (548 million) in 2045 (Saeedi et al. 2019). Furthermore, diabetes and its microvascular and macrovascular complications have become a heavy economic burden on the patients, their families, the health system, and the country. The estimated global diagnosis and treatment costs on diabetes are USD 760 billion in 2019, and they are expected to increase to a projected USD 825 billion in 2030 and USD 845 billion in 2045 (Williams et al. 2020). It has been found that cardiovascular risk is 2–4 times increased in adults with diabetes compared with those without diabetes, and the risk increases with worsening glycemic control. Diabetes caused 4.2 million deaths in year 2019, 11,666 people per day, and 8.10 people per minute (Meo et al. 2021). It is also connected with 75% increase in mortality rate in adults (Dal Canto et al. 2019). Chronic and serious hyperglycemia can result in the development of both microvascular and macrovascular complications. These complications include retinopathy, neuropathy, nephropathy, and an increased incidence of atherosclerotic diseases such as coronary heart disease and ischemic stroke (Harding et al. 2019; Forbes and Cooper 2013). Therefore, T2DM involves and impairs multiple physiological functions of various cells, tissues, organs, and systems of the body, with wide ranging serious health problems (Wu et al. 2018). The etiology of T2DM is not well known. Several identified risk factors include age, sedentary lifestyle, physical inactivity, calorie dense diets, obesity, and a broad array of both common and rare genetic variants (Scheen 2003; Barzilai et al. 1999; Flannick et al. 2019). In addition, an increasing body of evidence implicates that environmental chemicals are associated with the increasing epidemic of T2DM. Currently, diabetes ranks top on the international health agenda due to it being a main global issue that significantly damages human health and worldwide economies (Wang et al. 2018b). A number of countries across the world have developed strategies to interpose regarding behavioral risk factors such as encouraging healthy lifestyle, quit smoking, low-fat diet, fast food culture, and physical activity, to decrease the high prevalence of diabetes. However, these intervention efforts pay less role of occupational-related environmental pollution (Mohammad et al. 2018).

Endocrine-disrupting chemicals (EDCs) are natural or man-made chemicals. Because their structure is similar to steroid hormones, they can interact with the receptors of estrogen, androgen, and progesterone, interfere with any aspect of the role of endogenous hormones, including the biosynthesis, metabolism, transport, elimination, or receptor binding of endogenous hormones, thereby increase the risk of endocrine and metabolic diseases in humans and animals (Rutkowska et al. 2015; Gore 2016; Kiyama and Wada-Kiyama 2015; Silver et al. 2011; Alonso-Magdalena et al. 2011). An endocrine disruptor can be defined as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" (Zoeller et al. 2012). Several unique features of EDCs may distinguish them from other common chemicals. EDCs also include various lipophilic compounds, which mainly accumulate in lipid-containing tissues, such as adipose tissue, bind to lipids and move in the body (Yang et al. 2017). EDC can bind to endocrine receptors to activate, block, or change the synthesis and degradation of natural hormones. These actions occur through a variety of mechanisms, resulting in "false" lack or abnormal hormone signals, thereby increasing or inhibiting normal endocrine function (Zoeller et al. 2012). Data from ecological investigations, animal experimental models, clinical observations, and epidemiological surveys in humans agree to consider EDC as a significant risk factor for wildlife and human health (Heindel et al. 2015b). The large amount of

xenobiotics used in daily life and released into the environment through human activities may destroy the endocrine system of wild animals and humans at ecologically relevant concentrations. Currently, the EDC list includes hundreds of compounds, and it is still increasing. In one examination by the US Food and Drug Administration, more than 1800 chemicals that disrupt at least one of three endocrine pathways (estrogen, androgen, and thyroid) were identified (Ding et al. 2010). As reported by the European Union, out of a total of 564 chemicals recommended by various organizations as suspected EDCs in published papers or reports, 147 are considered likely to persist in the environment or be produced in large quantities (Kunysz et al. 2021). Among them, the biggest health problem is related to plasticizers [phthalates and bisphenol A (BPA) and its derivative bisphenol S (BPS)] and pesticides: dichlorodiphenyltrichloroethane (DDT), chlorpyrifos, methoxychlor, fungicides (vinclozolin), herbicides, polychlorinated biphenyls, brominated flame retardants, perfluoroalkyl and polyfluoroalkyl substances, industrial chemicals including alkylphenols, metals and dioxins, air pollutants such as polycyclic aromatic hydrocarbons (Street et al. 2018). In addition, new chemicals and/or compounds constantly enter the market every year, the vast majority of them are developed with poor or inappropriate toxicological testing for the detection of potential endocrine disruption. Therefore, a reliable estimate of the number of EDCs is practically impossible (Kunysz et al. 2021; Kassotis et al. 2020). Currently, an increasing body of evidence suggests that the increased prevalence of non-communicable diseases is related to EDC exposures; these diseases include endometriosis, infertility, premature puberty, susceptibility to infections, autoimmune diseases, neurodegenerative diseases, attention-deficit hyperactivity disorder (ADHD)/learning disabilities, asthma, heart disease, obesity, diabetes, and cancers (Kunysz et al. 2021). In May 2014, a seminar held in Parma produced The Parma Consensus Statement, proposing the hypothesis of metabolic disrupting chemicals, assumes that many endocrine disruptors can promote dyslipidemia, abnormal glucose metabolism, fatty liver, obesity, and diabetes in humans and animals (Kunysz et al. 2021). Overall, these metabolic changes may play an important role in the global epidemics of obesity, T2DM, and metabolic syndrome (MetS).

There are strong evidences obtained from experimental studies indicating the potential action of several environmental chemicals to induce endocrine disruption at environmentally relevant exposure levels. Indeed, like the endogenous hormones, EDCs can produce big effects on development at very low dose levels of exposure (parts per billion and parts per trillion) because prenatal and early postnatal are the most vulnerable periods of life. Both gene suppression and gene activation have been observed in prenatal and early postnatal exposure (Vom Saal 2016). Some human birth cohort studies and animal experimental observations have shown that exposure to EDCs during the critical periods of fetal development can alter the growth and metabolism of the fetus, and subsequently promote metabolic disorders in adulthood (Chamorro-García and Blumberg 2014; Veiga-Lopez et al. 2018; Desai et al. 2015). In particular, a lot of previous studies have shown that these EDCs are associated with an increased risk of obesity, T2DM and MetS (Desai et al. 2015; Anderson et al. 2017; Neel and Sargis 2011; Marraudino et al. 2019). Therefore, this paper aims to review the current progress in the association between exposure to EDCs and T2DM. The identification of the association between EDC exposures and T2DM in different populations may provide new insights of diabetes pathogenesis and new targets of early prevention.

Diabetes-Related EDCs

EDCs contain a heterogeneous set of synthetic and natural compounds, most of which have phenolic groups in their structure, giving them an affinity for steroid hormone receptors such as estrogen, progesterone, and androgens. EDCs have agonistic or antagonistic effects on nuclear receptors, which are their main targets (Skinner 2011). These chemical compounds can enter the human body through ingestion, inhalation, and skin absorption (Rudel and Perovich 2009). They penetrate into soil and groundwater, and enter the food chain by accumulating in fish, animals, and plants. Some consumer products such as household chemicals, cosmetics, fragrance products, lotions, antibacterial soaps, and fabrics rich in flame retardants may be packaged in containers that can leach EDCs. Food processing may accumulate traces of EDCs leached from manufacturing and storage materials. EDCs such as lead in furniture, flame retardants, and polychlorinated biphenyls can pollute household dust. Some lipophilic EDC can remain in the human body for many years, and is secreted from fat cells, and then binds to the appropriate receptor to change the hormone response. Continuous daily exposure to EDC mixtures, whose concentrations are even lower than the human body's established tolerance threshold for individual substances, will also significantly increase the risk of women and men suffering from hormonal and metabolic disorders such as diabetes (Sargis and Simmons 2019). In addition, the development of modern civilization and the increasing demand for new chemicals have increased our exposure to EDCs. The widespread production and common use of these chemical substances in daily life leads people to constant exposure to harmful substances in the environment, including furniture, paint, floors, electronic equipment, and toys. Additional daily contact occurs through the release of these substances from commonly used items such as food packaging, bottled beverages, cosmetics,

receipts, clothes, food, contact lenses, and dental seals (Żwierełło et al. 2020; Beszterda and Frański 2018). Certain EDCs may be even more common in newborns and children than in adults because they are associated with greater consumption of specific foods and water. In addition, infancy and adolescence have higher ventilation rates, intestinal absorption, surface area-to-volume ratios, and hand-to-mouth activity than adults (Selevan et al. 2000). Breastfeeding is also associated with more infants' exposure to EDCs (Grandjean and Jensen 2004). Generally speaking, both organochlorines and organophosphorus are the most widely studied insecticides related to obesity and/or T2DM in humans and rodents (Xiao et al. 2017). The principal diabetes-related EDCs are listed in Table 1.

Bisphenol A

Bisphenol A (BPA), a ubiquitous EDC, is the major component of polycarbonate plastics. It is one of the first compounds identified as endocrine disruptor, which can disrupt the endocrine system and produce effects very similar to MetS (Pérez-Bermejo et al. 2021). It is used in the manufacture of epoxy resins, food can linings, recycled paper, carbon-free cash register receipts, compact discs (CD) and digital video CD coatings, electronic equipments, and toys (Chailurkit et al. 2017; Rubin 2011). The BPA in these products can react with chlorinated tap water to form chlorinated BPA derivatives (Andra et al. 2015). Humans are constantly exposed to small quantities of BPA via many routes (Farrugia et al. 2021). Regardless of age or gender, BPA can enter the human body through breathing, digestion, and transdermal routes, and pass from mother to offspring through the placenta or breast milk (Lee et al. 2018). Although it is a non-persistent EDC with a short half-life, more than 90% of individuals can detect it in the urine (Song et al. 2016). Pharmacokinetic investigations in humans have shown that after a single exposure through ingestion, BPA will be rapidly combined in the liver and excreted through bile and urine, with a half-life of about 5.3 h (Völkel et al. 2002). BPA is a xenoestrogen. Its structure is similar to endogenous 17β-estradiol. It can bind to and exert effects through extranuclear estrogen receptors (ERα and ERβ) at environmentally relevant doses (Alonso-Magdalena et al. 2008; Soriano et al. 2012), and then change

Table 1 List of principal diabetes-related endocrine-disrupting chemicals (EDCs)

EDC	Abbreviation	T2DM	Site of action/others
Bisphenol A	BPA	√√√	Steroid receptors (xenoestrogen), PPARs, RXR
di-2-ethylhexyl phthalate	DEHP	√√√	Promotes expression of adipogenic genes
Tributyltin	TBT	√√√	PPARγ and RXRα activator
Polychlorinated biphenyls	PCBs	√√√	Aryl hydrocarbon receptor
Hexachlorobenzene	HCB	√√√	Plasma HCB concentration was positively associated with incident T2DM
Bisphenol S	BPS	√√√	The activator of PPARγ, it can upregulate lipoprotein lipase and CAAT/enhancer-binding proteins β expression
Dichlorodiphenyltrichloroethane	DDT	√√	Steroid receptors
dichlorodiphenyldichloroethylene	DDE	√√	The main metabolite of the insecticide DDT
2,3,7,8-Tetrachlorodibenzo-p-dioxin	TCDD	√√	Aryl hydrocarbon receptor
Benzo(a) pyrene	BaP	√√	
perfluoroalkyl substances	PFAS	√√	
dibutyl phthalate	DBP	√√	Similar steroid receptors, PPARs, RXR; disrupting the PI3K expression and AKT phosphorylation
Polybrominated biphenyl ethers	PBDEs	√	PBDE congener 153 (PBDE-153) was positively associated with increased risk of gestational diabetes mellitus
Perfluorooctanoate	PFOA	√	Positive associations with gestational diabetes mellitus with a family history of T2DM
Perfluorooctane sulfonate	PFOS	√	Higher serum PFOS levels may be a biomarker of exposure and susceptibility to develop T1DM
Atrazine		√	A triazine herbicide; $C_8H_{14}ClN_5$ or 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine
Tolylfluanid	TF	√	
Phthalates	PAEs	√	Steroid receptors (antiandrogen), PPARs and RXR

Abbr abbreviation; *PPARs* peroxisome proliferator-activated receptors; *RXR* retinoid X receptor; *RXRα* retinoid X receptor α

√ (the strength of the evidence), one article in animal or human; √√, one paper in animal and human or more than one paper in either animal or human; √√√, more than one thesis in both animal and human, or multiple treatises in animal studies

various aspects of β-cell metabolism by regulating estrogen receptor signaling pathway (Alonso-Magdalena et al. 2006; Nadal et al. 2009). The expression of ERs in the body is very extensive, and many tissues have high expression of ERs, including breast, ovary, prostate, testis, liver, pancreas, brain, bone marrow, and adipose tissue (Lee et al. 2012). In vitro, BPA can act as an ER antagonist at concentrations below 10 nM, or as an ER agonist at concentrations above 10 nM in a cell-type-specific manner (Li et al. 2012; Acconcia et al. 2015). Additionally, BPA also acts through G protein-coupled receptor 30 (GPR30; also called 7-transmembrane G protein-coupled receptor) that mediates rapid non-genomic signal transduction of estrogen (Dong et al. 2011; Prossnitz et al. 2008). BPA has a relatively high affinity for GPR30. The combination between BPA and GPR30 can induce a rapid activation of the MAPK/ERK signaling pathways (Völkel et al. 2002; Thomas and Dong 2006). It has also been shown to inhibit the release of adiponectin and promote angiogenesis on the endothelium (Andersson and Brittebo 2012; Hugo et al. 2008). Adiponectin has insulin sensitivity, anti-atherosclerosis, and anti-inflammatory properties. Hypoadiponectinemia is associated with insulin resistance and T2DM (Okamoto et al. 2002; Matsuda et al. 2002; Yamauchi et al. 2001; Kaser et al. 2008). BPA also increases the expression of a variety of pro-inflammatory adipocytokines through GPR30, including interleukin 6 (IL-6) and monocyte chemotactic protein 1 (MCP1) (Cimmino et al. 2019). It has been shown that different concentrations of BPA in vivo and in vitro can disrupt glucose homeostasis and pancreatic β-cell function by altering gene expression and mitochondrial morphology. As a risk factor for obesity and diabetes, it has recently obtained attention in the scientific community. In addition, BPA is also associated closely with the development of insulin resistance, and long-term adverse metabolic effects following fetal and perinatal exposures (Farrugia et al. 2021). A number of cross-sectional studies (Silver et al. 2011; Lang et al. 2008; Soundararajan et al. 2019; Melzer et al. 2010; Shankar and Teppala 2011; Haq et al. 2020; Beydoun et al. 2014; Wang et al. 2012), case–control researches (Ahmadkhaniha et al. 2014; Duan et al. 2018; Stahlhut et al. 2018; Li et al. 2018; Murphy et al. 2019), prospective investigations (Sun et al. 2014; Rancière et al. 2019), and meta-analyses (Song et al. 2016; Rancière et al. 2019; Hwang et al. 2018) have showed that there is a significant association between BPA and the development of insulin resistance, impaired glucose homeostasis, and T2DM in different ethnic groups or populations. Higher BPA concentrations in serum or urinary samples were positively correlated with an increased risk of prediabetes and T2DM (Sabanayagam et al. 2013). The incidence of T2DM in the participants was higher in the highest quartile of BPA levels than in the lower quartiles. A recent meta-analysis consisting of 16 studies, 41,320 subjects showed that BPA concentrations measured in urine (OR 1.20, 95% CI 1.09, 1.31) or serum (OR 1.28, 95% CI 1.14, 1.44) were positively associated with the risk of T2DM (Hwang et al. 2018). However, no association between BPA exposure and T2DM risk was noted in many population-based epidemiological surveys (Chailurkit et al. 2017; Andra et al. 2015; Lakind et al. 2014; Ning et al. 2011; Kim et al. 2013; Casey and Neidell 2013; Piecha et al. 2016; Watkins et al. 2016; Wang et al. 2019a; Shu et al. 2018; Bi et al. 2016). In summary, the extensive body of evidence outlined above has provided insight into the multiple mechanisms by which BPA regulates physiological pathways associated with the development of T2DM. BPA acts on multiple tissues involved in regulating glucose homeostasis. It can positively or negatively regulate pancreatic insulin release and secretion, and alter β-cell gene expression, electrical activity, and β-cell survival. This is a consequence of dysregulated β-cell gene expression. BPA exposure for 24 h results in a downregulation of the pancreatic glucose transporter (SLC2A2) and glucokinase (GCK, it catalyzes the phosphorylation of glucose to glucose-6-phosphate), and consequently reduced insulin secretion. The decreased expression of GCK and SLC2A2 is the result of downregulation of key β-cell genes, including insulin promoter factor 1 (PDX1), and hepatocyte nuclear factor 1A (HNF1A). The synaptosome-associated protein of 25 kDa (SNAP25) expression is also decreased in response to BPA (Farrugia et al. 2021). This affects adipocytokine function, modulates hepatic and muscle insulin sensitivity, stimulates de novo lipogenesis, and acts on central nervous system pathways that regulate feeding and systemic metabolism (Farrugia et al. 2021).

Phthalates

Phthalates are the diesters of 1,2-benzendicarboxylic acid. They can classify into low and high molecular weights. Low-molecular-weight phthalates are mainly used in personal care products and cosmetics, but they are also widely used in pesticides and food packaging plastics. High-molecular-weight phthalates include several compounds that are mainly used to make plastics more flexible and durable, therefore as a plasticizer in polyvinyl chloride materials. Among them, the most commonly used additive is di-2-ethylhexyl phthalate (DEHP) (Wang et al. 2019b). As we all know, phthalates may migrate, leach, or evaporate into indoor air and atmosphere, foods, and other goods, etc., and then become a source for human uptake because they are not covalently bound to the plastic (Shu et al. 2019). Phthalates have been detected in a variety of industrial and consumer products. Many daily products such as clothing, toys, packaging materials, wallpaper, paints, floors, roof paints, adhesive coatings, sealants, and cables contain phthalates (Shu et al. 2019; Afshari et al. 2004). They can enter human body through

inhalation, ingestion, or skin absorption. In addition, phthalates can cross the placenta and cause fetal exposure (Buckley et al. 2016; Rudel et al. 2011). The association between DEHP exposure and pancreatic β-cell dysfunction in both sexes has been observed in several experimental investigations (Rajesh et al. 2014b; Campioli et al. 2014). Most of the human epidemiological surveys related to insulin resistance, obesity, and diabetes are from the National Health and Nutrition Examination Survey (NHANES) in the USA. In a previous cross-sectional study, James-Todd et al. (2012) showed that several urinary phthalate metabolite concentrations such as monobenzyl phthalate (MBzP), mono-(3-carboxypropyl) phthalate (MCPP), mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), and three di-(2-ethylhexyl) phthalate metabolites were associated with the prevalence of diabetes among women. Women with higher levels of phthalate metabolites were more likely to develop diabetes than those with the lowest levels of phthalate metabolites after adjusting for potential confounding factors. Women in the highest quartile of MBzP and MiBP are almost twice the odds of diabetes [OR 1.96 (95% CI 1.11, 3.47) and OR 1.95 (95% CI 0.99, 3.85), respectively] compared with those in the lowest quartile. MnBP and the three bis (2-ethylhexyl) phthalates were positive correlation, while MCPP seemed to have a threshold effect. In a previous cross-sectional study, Lind et al. (2012) also found that several phthalate metabolites such as monoethyl phthalate, monomethyl phthalate, and MiBP, but not mono(2-ethylhexyl) phthalate were associated with an increased prevalence of T2DM in the elderly. These phthalate metabolites may also be the markers of insulin secretion and resistance. The exact mechanism of action of phthalates and their metabolites is not fully understood, but they may increase the risk of T2DM by activating peroxisome proliferator-activated receptors (Casals-Casas and Desvergne 2011; Sarath Josh et al. 2014). These receptors are the main regulators of lipid and glucose homeostasis (Evans et al. 2004), by impairing the development and progression of pancreatic β-cells.

Chlordane Compounds

Chlordane compounds (CHLs) are the components of industrial chlordane listed in the Stockholm Convention on Persistent Organic Pollutants (Patterson et al. 2009). The main ingredients are heptachlor (5%), *trans*-nonachlor (5%), *cis*-chlordane (11%), and *trans*-chlordane (13%). In addition, more than 30 chemicals with less content were also identified (Mattina et al. 1999). Chlordane is a synthetic organochlorine pesticide that has been used in agriculture for decades, but it is also used for pest control (Fisher 1999). In humans, exposure mainly occurs through food intake, but it also occurs through inhalation or skin contact (Singh et al. 2019). In the past few decades, as people have become more aware of the role of the environment in health, environmental chemical exposure has caused great concern. Although CHLs were discontinued globally in 1997, due to their ability to accumulate in the environment and migrate long distances from where they were released, chlordane-related compounds still exist in soil, air, and water (Mattina et al. 2002; Wang et al. 2015; Jantunen and Bidleman 1998). Although the exposure levels of CHLs are expected to decrease over time due to the reduction in its use, its harmful consequences may still be felt for a long time. As a category of EDCs, CHLs may disrupt the biosynthesis, metabolism, or action of endogenous hormones resulting in an unbalanced hormonal function. An increasing scientific evidence shows that CHLs are the risk factors for the pathogenesis and development of obesity and T2DM (Evangelou et al. 2016; Tang-Péronard et al. 2011).

A number of previous studies have showed that there are associations between oxychlordane (Everett et al. 2010; Son et al. 2010; Park et al. 2010; Lee et al. 2006, 2007a, 2007b, 2010; Airaksinen et al. 2011; Cox et al. 2007; Rylander et al. 2015; Grice et al. 2017; Eden et al. 2016; Zong et al. 2016), *trans*-nonachlor (Everett et al. 2010; Son et al. 2010; Park et al. 2010; Lee et al. 2006, 2007a, 2007b, 2010; Airaksinen et al. 2011; Cox et al. 2007; Rylander et al. 2015; Grice et al. 2017; Eden et al. 2016; Zong et al. 2016; Lind et al. 2011; Han et al. 2020), heptachlor (Tang-Péronard et al. 2011; Everett and Matheson 2010; Son et al. 2010; Patel et al. 2010; Starling et al. 2014), chlordane (Starling et al. 2014), and diabetes in different populations. More recently, a meta-analysis of 31 eligible studies showed that the odds of having diabetes among adults were significantly increased with increasing levels of chlordanes. The estimates were statistically significant for heptachlor epoxide [OR 1.88 (95% CI 1.42–2.49)], oxychlordane [OR 1.96 (95% CI 1.19–3.23)], and trans-nonachlor [OR 2.43 (95% CI 1.64–3.62)] (Mendes et al. 2021).

Parabens

Parabens are alkyl esters of p-hydroxybenzoic acid. They are used as antibacterial preservatives in a range of consumer products such as cosmetics, pharmaceuticals, and foods (Liao et al. 2013). They are another group of EDCs (Błędzka et al. 2014; Boberg et al. 2010). They are esters of p-hydroxybenzoic acid with alkyl substituents ranging from methyl to butyl or benzyl groups in chemistry. The most commonly used parabens are benzylparaben (BeP), butylparaben (BuP), ethylparaben (EtP), methylparaben (MeP) as well as propylparaben (PrP). Parabens can be absorbed through ingestion, inhalation, and skin. Due to daily use of products containing parabens, they may accumulate in the body. In a previous study from China, 13 categories of food samples ($n = 282$) from nine cities could detect six

paraben contents. These samples included eggs, fish and seafood, meat, bean products, dairy products, cereals and their products, vegetables, fruits, beverages, cookies, cooking oils, condiments, and others. Almost all food samples could detect at least one of the analyzed parabens, the detection rate was 99%. The total contents of six parabens ranged from below limit of quantification to 2530 ng/g fresh weight, with a mean value of 39.3 ng/g. MeP, EtP, and PrP were the major paraben analogs in the samples, accounted for 59%, 24%, and 10% of total paraben contents, respectively (Liao et al. 2013). The cytotoxic mechanism of parabens may be related to mitochondrial failure, which depends on the induction of membrane permeability transitions, accompanied by mitochondrial depolarization and the decoupling of cellular adenosine triphosphate (ATP) through oxidative phosphorylation (Soni et al. 2002). Some epidemiological surveys point that paraben exposures are associated with T2DM. In a previous case–control study (Li et al. 2018), urinary concentration of parabens in 101 individuals from Jeddah, Saudi Arabia was measured to examine the association between parabens and T2DM. After adjusting for potential confounding factors, urinary MeP, EtP, and PrP levels were higher in T2DM cases than in control group. Compared with the first quartile, individuals whose urinary concentrations of MeP, EtP, and PrP were in the fourth quartile showed over a sixfold increase in the odds of having T2DM. In the sub-sample of Granada EPIC-Spain cohort ($n = 670$), Salamanca-Fernández et al. (2020) analyzed the potential associations between non-persistent environmental pollutants and T2DM risk. Serum concentrations of MeP, EtP, PrP, and BuP were quantitatively analyzed. The median follow-up time was 23 years. A total of 182 patients (27%) in the sub-cohort were diagnosed as T2DM. MeP is the most frequently detected non-persistent environmental pollutants, 88.42% of the samples exceeded the detection limit, and the detection rate of BuP was the lowest (19.21%). Those individuals within the fourth PP quartile (0.53–9.24 ng/ml) had a statistically significant increase in the risk of T2DM (HR 1.668, $P = 0.012$). Kim et al. (2020) examined whether exposure to parabens was associated with obesity, MetS, or its components among Canadians. MeP, EtP, PrP, and BuP concentrations were measured in the urine. There was a positive association between paraben exposures and MetS in men. A tenfold increase in PrP content was associated with a 40% (95% CI 3–90) higher prevalence of MetS among men, whereas EtP was associated with a 63% (95% CI 2–86) lower prevalence among women. Recently, Lee et al. (2021) also showed that the risk of T2DM was significantly higher in the highest quartiles of MeP and EtP than in the lowest quartiles following covariate-adjusted standardization [OR (95% CI) 1.68 (1.08–2.60) and 2.74 (1.77–4.24), respectively]. These findings suggest that several parabens were potential risk factors for T2DM. Liu et al. (2019a) investigated whether exposure to MeP, EtP, PrP, BuP, and BeP in early pregnancy is related to gestational diabetes mellitus (GDM). Compared with the lowest quartile, urinary EtP concentration was associated with GDM after adjustment for potential confounders. The risk ratio (RR) was 1.12 (95% CI 0.63–2.01) for the second quartile, RR was 1.11 (95% CI 0.64–1.93) for the third quartile, and RR was 1.70 (95% CI 1.02–2.82) for the highest quartile. In different studies from diverse populations, however, the association between parabens and T2DM is inconsistent. Li et al. (2019) reported that the detection rates of MeP, EtP, PrP, BuP, and benzyl-substituted para-hydroxybenzoic acid ester (BzP) in the urinary samples were 97.70%, 71.26%, 96.55%, 15.80%, and 2.73%, respectively. But no significant association was found between parabens and GDM among the overall population. Bellavia et al. (2019) also found that 1st trimester BuP and PrP urinary concentrations were associated with glucose levels in a pregnancy cohort of women at high risk of GDM after adjusting for potential confounders. Among a nationally representative sample of US adults, however, Ward et al. (2020) showed that the higher urinary concentrations of PrP, BuP, EtP, and MeP were associated with lower odds of diabetes. The adjusted ORs (95% CI) of diabetes comparing the 75th to 25th percentiles of each paraben were 0.71 (0.61–0.83) for PrP, 0.66 (0.54–0.80) for BuP, 0.60 (0.51–0.71) for EtP, and 0.79 (0.68–0.91) for MeP.

Pesticides

Pesticides have brought many benefits to humans in the fields of agriculture, industry, and health, but their toxicities to both humans and animals have always been a worrying issue. Most of the disorders induced by pesticides are related to organophosphorus, organochlorines, phenoxyacetic acids, and triazine compounds. According to the toxicities, pesticides can be divided into different categories such as pulmonary, neurological, reproductive, developmental, and metabolic toxicity and carcinogenicity. Although acute poisoning is common for certain types of pesticides such as organophosphorus, the association between long-term and sublethal pesticide exposure and some persistent disease epidemics will become a global concern (Mostafalou and Abdollahi 2017). There are many ways for humans to be exposed to pesticides, including occupational, environmental, residential, parental, maternal, and paternal. To date, the evidences of association between pesticide exposures and T2DM are still ambiguous. Positive associations have been reported between polychlorinated dibenzodioxins, dibenzofurans, polychlorinated biphenyls, dichlorodiphenyldichloroethylene (DDE), oxychlordane, trans-nonachlor, hexachlorobenzene (HCB), hexachlorocyclohexane exposures, and the risk of T2DM (Jaacks and Staimez 2015; Czajka et al. 2019; Lind and Lind 2018). In a small-sample exploratory

study, Son et al. (2010) investigated the associations between β-hexachlorocyclohexane (β-HCH), HCB, heptachlor epoxide, p,p′-DDE, p,p′-dichlorodiphenyldichloroethane (DDD), p,p′-DDT, o,p′-DDT, oxychlordane, trans-nonachlor, and mirex and the risk of T2DM in Koreans. Although the absolute concentrations of organochlorine pesticides were not higher than those of other populations, the low-dose background exposures of heptachlor epoxide, oxychlordane, p,p′-DDT, and p,p′-DDT were closely related to the prevalence of T2DM in Koreans, indicating that Asians may be more sensitive to the toxic effects of organochlorine pesticides than other races. In a recent cross-sectional study, Park et al. (2019) used data from the Korean Farmer Cohort Study ($n = 2559$), and studied the association between pesticide exposure and the prevalence of diabetes in Korean rural populations. At baseline, the prevalence of diabetes was 9.30%. After adjusting for covariates, pesticide exposure was associated with diabetes risk. Stratified analysis according to body mass index (BMI) showed that all variables related to pesticide exposure were associated with the prevalence of diabetes in the overweight or obese individuals, whereas no significant correlation was observed in normal body weight, indicating that pesticide exposure was associated with the prevalence of diabetes in Koreans, especially in the overweight or obese individuals. In a population-based case (T2DM, $n = 866$)-controlled (healthy controls, $n = 1021$) study conducted in Thailand, Juntarawijit and Juntarawijit (2018) showed that the prevalence of diabetes was positively associated with exposure to fungicides, herbicides, insecticides, molluscicides, and rodenticides (OR 1.35; 95% CI 1.04–1.76) after adjusting for age, gender, BMI, alcohol consumption, cigarette smoking, occupation, and family history of diabetes. Among 35 individual brand-named pesticides investigated, endosulfan (OR 1.40; 95% CI 1.01–1.95), mevinphos (OR 2.22; 95% CI 1.17–4.19), carbaryl/Sevin (OR 1.50; 95% CI 1.02–2.19), and benlate (OR 2.08; 95% CI 1.03–4.20) were found statistically significant ORs. The impact of long-term exposure to environmental persistent organic pollutants on the risk of MetS has been evaluated by Mustieles et al. (2017). The study also was combined with a cross-sectional and 10-year longitudinal follow-up design. After adjusting for confounding factors, β-HCH and HCB were independently associated with increased risk of metabolic impairment (OR 1.17, 95% CI 1.01–1.36 and 1.17, 95% CI 0.99–1.38, respectively), indicating that past exposure to β-HCH and HCB has always been associated with the risk of metabolic disorders. In a systematic review and meta-analysis of 22 observational studies, Evangelou et al. (2016) showed that there was an association between exposure to organochlorine pesticides and T2DM. Exposure to any type of pesticides and T2DM have a total OR of 1.58 (95% CI 1.32–1.90, $P = 1.21 \times 10^{-6}$) between the highest tertile and the lowest tertile, with large heterogeneity ($I^2 = 66.8\%$). In particular, studies evaluating T2DM ($n = 13$ studies) showed a similar summary effect when comparing the top and bottom tertiles of exposure: 1.61 (95% CI 1.37–1.88), $P = 3.51 \times 10^{-9}$), there is no heterogeneity ($I^2 = 0\%$). According to the analysis of pesticide types, chlordane, heptachlor, HCB, pp-DDD, pp-DDE, and trans-nonachlor increase the risk of T2DM. In a low-exposed population dominated by subsistence farmers in Nepal, however, Hansen et al. (2020) did not find the association between pesticide exposure and T2DM. Lower odds of T2DM (adjusted OR 0.68, 95% CI 0.52–0.90) were found among persons reporting any pesticide exposure compared to those reporting no pesticide exposure. In addition, the exposure–response relationship was not found between pesticide exposure and T2DM. In summary, these cross-sectional studies may have potential limitations, because few studies involve selection bias and confounding factors, and most effect estimates have very wide confidence intervals. In fact, it is difficult to study the direct effects of different pesticides on animals or humans (He et al. 2020).

Other Diabetes-Related EDCs

In addition, other types of insecticides have also been associated with the development of obesity and/or T2DM in animals or humans (Mesnage et al. 2018; Wei et al. 2019). These insecticides include carbamates, neonicotinoids, pyrethroids, and 2,3,7,8-tetrachlorodiphenyl-p-dioxin (TCDD). In particular, both pyrethroids and neonicotinoids have been known as the risk factors for obesity and T2DM, respectively, involved in enhancing adipogenesis and/or altered glucose responsiveness (Shen et al. 2017). TCDD belongs to the dioxin family of environmental poisons. It is introduced into the environment as a by-product of industrial processes (such as incineration and burning of fossil fuels), but it can also come from natural processes, such as volcanic eruptions and forest fires. In humans and animals, ingestion of food contaminated with TCDD is the main source of dioxin exposure. Once TCDD enters the body, it is chemically stable and is not easily metabolized in most species. In humans, TCDD has a half-life of 8 years and is highly resistant to either biological or chemical degradation (Sorg et al. 2009). Therefore, dioxin has significant environmental persistence and bioaccumulation. Among occupationally exposed populations in New Zealand, TCDD was associated with an increased risk of diabetes and a series of subclinical reactions in multiple systems. Diabetes was more common in people who worked with TCDD exposure (OR 4.0, 95% CI 1.0–15.4) and people with serum TCDD ≥ 10 pg/g (OR 3.1, 95% CI 0.9–10.7). Non-fasting blood glucose levels > 6.6 mmol/l were more common among those working with TCDD exposure (OR 3.6, 95% CI 1.0–12.9) ('t Mannetje et al. 2018). Perfluoroalkyl and polyfluoroalkyl

substances (PFASs) are synthetic fluorinated compounds. They are used in the manufacture of industrial and consumer products such as antifouling and non-stick coatings for furniture, food packaging, pesticides, and firefighting foams (Lau et al. 2007). Due to stable carbon–fluorine bonds (Olsen et al. 2007), PFASs can persist in the environment and body for 2–5 years or more. In humans, exposure to PFASs is common through dietary intake of contaminated food or drinking water. Certain PFASs can cross the placenta. Many experiments have shown that PFASs can alter estrogen and androgen receptor function, activate peroxisome proliferator-activated receptors (PPARs), and disrupt thyroid hormone homeostasis, all of which have known regulatory roles in metabolic function (Aris et al. 2018). Several cohort and case–control studies have also obtained compelling evidences about exposure to perfluorinated and polyfluoroalkyl substances (PFAS) during pregnancy, including short-chain alternatives, which will lead to GDM and IGT in pregnant women from China (Liu et al. 2019b; Wang et al. 2018a, 2018c), USA (Zhang et al. 2015; Rahman et al. 2019), Canada (Shapiro et al. 2016), Denmark (Jensen et al. 2018), or Spain (Matilla-Santander et al. 2017).

EDC Exposure and Gestational Diabetes Mellitus

GDM is defined as glucose intolerance that is first diagnosed in pregnancy (American Diabetes Association 2011). It is one of the most common pregnancy complications and has an important impact on the health of mother and child. GDM only represents a relatively high blood glucose level at a certain point in the life of young women because its definition does not require any return to normal blood glucose levels after delivery. The overall incidence of GDM was approximately 15% of pregnancies (Coustan et al. 2010) or 10%. The incidence was higher in Asian (17%) and Hispanic (11%) than in non-Hispanic white (7%) and black (7%) females (Xiang et al. 2011). Maternal hyperglycemia will increase the transfer of transplacental glucose to the fetal circulation, leading to excessive stimulation of the fetal pancreas. Physiologically, insulin does not pass through the placenta, and the fetus begins to produce its own insulin around 9 weeks of age. Fetal hyperinsulinemia can aggravate fetal metabolism and excessive growth of muscle tissue including myocardium, adipose tissue, and liver, and increase the demand for oxygen, especially in the final stages of pregnancy. Therefore, fetuses with GDM in pregnancy are more likely to suffer from intrauterine hypoxia and perinatal injury due to excessive birth weight. Exposure of pregnant women to EDCs may be a reason for the increased incidence of GDM. Increasing evidence from cohort and case–control studies indicates that EDC has a potential role in inducing GDM. In a previous study, Li et al. (2019) showed that moderately higher levels of PrP and total estrogenic activity of parabens were significantly associated with an increasing GDM prevalence among the overweight/obese pregnant women, suggesting that they were a subgroup more prone to GDM. Moreover, a study conducted by Shaffer et al. (2019) found that T1T3avg monoethyl phthalate was significantly associated with increased odds of developing GDM. In addition, phthalate metabolites were also found to be related to glucose intolerance, with possible stronger associations in certain racial/ethnic subgroups such as Asians. In a recent cross-sectional study, Hou et al. (2021) demonstrated that 2-tert-octylphenol (2-t-OP) exposure was associated with higher risk of GDM, whereas nonylphenol (NP) exposure was associated with lower risk of GDM. But no statistically significant association was observed between phthalates or BPA with IGT or GDM (Shapiro et al. 2015). Both bisphenols and parabens have also been identified as EDCs that might cause GDM, but the evidence for this association is sparse.

The increasing incidence of GDM almost coincides with the widespread use of EDCs. The extensive production and widespread use of these EDCs in daily life lead people to constant exposure to harmful chemicals in the environment. Although its pathogenesis of GDM is not very clear, EDCs, i.e., BPA may change the function of pancreatic β-cells and energy homeostasis of the body, eventually increase the risk of GDM. BPA disturbs the function of pancreatic β-cells, which leads to a failure of compensatory mechanisms and the development of hyperglycemia (Alonso-Magdalena et al. 2011; Gore et al. 2015; Mimoto et al. 2017). More importantly, EDC exposure during pregnancy may cause epigenetic changes, which may also be manifested and passed on to offspring many years later. Several model system studies have shown that external environmental EDC exposure can induce epigenetic mutations during gametogenesis, embryogenesis, and fetal development (Uzumcu et al. 2012; Tiffon 2018). Wei et al. (2017) revealed that BPA treatment resulted in impaired glucose tolerance and a compensatory increase of pancreatic islets insulin secretion and duodenal homeobox 1 (Pdx1) expression in mice. Inhibition of Pdx1 can reduce glucose-stimulated insulin secretion and ATP production in the pancreatic islets of BPA-exposed mice. miR-338 regulates Pdx1 and thus contributed to BPA-induced insulin secretion dysfunction from compensatory to decompensated. Short-term BPA exposure downregulates miR-338 by activating Gpr30, while long-term BPA exposure upregulates miR-338 by inhibiting the glucagon-like peptide 1 receptor (Glp1r). These results indicate that BPA regulates Gpr30/Glp1r to mediate the expression of miR-338, and its role is to control Pdx1-dependent insulin secretion. Therefore, the Gpr30/Glp1r-miR-338-Pdx1 axis may be a new mechanism of BPA-induced pancreatic insulin secretion dysfunction. It

is not clear whether BPA and phthalate exposure may alter the serum levels of miRNAs associated with GDM risk. In a recent study, Martínez-Ibarra et al. (2019) found that serum levels of miR-9-5p, miR-29a-3p, and miR-330-3p were higher in GDM patients than in non-diabetic subjects. Phthalates and BPA were detected in 97–100% and 40% of urine samples, respectively.

Although GDM usually resolves after childbirth, it may have many long-term health consequences, such as increased risk for T2DM and cardiovascular disease in the mother, as well as future metabolic and cardiovascular complications such as increased adiposity or even obesity, IGT, high blood pressure, hyperlipidemia and non-alcoholic fatty liver disease in the offspring, and premature delivery (female) (Lowe et al. 2018, 2019a; Liang et al. 2020; Davis et al. 2013; Miranda et al. 2019). The offspring of mothers with GDM may also increase the risk of long-term sequelae. Several epidemiological surveys have found higher rates of metabolic complications in youths who were exposed to maternal GDM (Holder et al. 2014; Dabelea et al. 2008; Blotsky et al. 2019). These long-term metabolic complications among offsprings who exposed to maternal GDM include insulin resistance, IGT, and T2DM. An increased risk of IGT in the offspring of mothers with mild, untreated hyperglycemia has been observed in the several previous studies (Tam et al. 2017; Lowe et al. 2019b; Scholtens et al. 2019). The study conducted by Holder et al. (2014) showed that the development of IGT or T2DM was higher in GDM exposed group than in GDM non-exposed group (31.1% vs. 8.6%, $P < 0.001$). GDM exposure was the most significant predictor of developing IGT or T2DM (OR 5.75, 95% CI 2.19–15.07, $P < 0.001$). In addition, the GDM exposed group displayed a reduction in β-cell function at both baseline and follow-up and in insulin sensitivity at follow-up compared with the GDM non-exposed group. Intrauterine exposure to maternal diabetes and obesity has been strongly associated with T2DM in African-American, Hispanic, and non-Hispanic white youths. After adjusting for offspring age, sex, and race/ethnicity, exposure to maternal diabetes (OR 5.7, 95% CI 2.4–13.4) and obesity (OR 2.8, 95% CI 1.5–5.2) were independently associated with T2DM (Dabelea et al. 2008). Blotsky et al. (2019) also found that incident diabetes in offspring during childhood and adolescence was associated with GDM. Incidence of pediatric diabetes was higher in offspring born to mothers with GDM (OR 4.52, 95% CI 4.47–4.57) than in mothers without GDM (OR 2.4, 95% CI 2.37–2.46). Among the women with mild GDM who were randomized to receive treatment or routine care, the fasting blood glucose level of their offsprings was significantly reduced (Landon et al. 2015), but childhood obesity or metabolic dysfunction did not decrease in their offsprings. Further evidence shows that exposure to hyperglycemia below the diagnostic criteria of GDM in utero increases the risk of glucose metabolism disorders in the future, which may be the result of adverse intrauterine fetal programming of the pancreas (Scholtens et al. 2019). However, there are also several studies failed to find the association between GDM exposure and insulin resistance or other glycemic outcomes in offspring (Gingras et al. 2018; Tam et al. 2010). Blood pressure levels, plasma lipid profiles, and the rate of abnormal glucose tolerance were similar in adolescent offspring of mothers with GDM and in control subjects (Tam et al. 2010). In addition, in the some intervention studies of metformin (± insulin) or insulin treatment of mild GDM, monitoring of offsprings' BMI, adiposity, and glucose tolerance do not demonstrate that GDM treatment significantly reduces adverse childhood metabolic outcomes (Rowan et al. 2018; Ijäs et al. 2015; Tertti et al. 2015).

Prenatal and Perinatal EDC Exposure and T2DM

Human studies have rightly given substantial attention to associations of prenatal exposure to EDCs with T2DM. During the critical periods of development, the susceptibility to hormone disorders caused by EDC exposure is particularly high. These critical periods of development include the prenatal, perinatal period, infancy, childhood, and adolescence. A hostile intrauterine environment associated with poor maternal life style may be a risk factor of offspring T2DM. Kern et al. (2002) examined the effects of TCDD on adipocytes. The addition of TCDD into cultural adipocytes can increase tumor necrosis factor (TNF) secretion and decrease glucose transport and lipoprotein lipase (LPL) activity. Since TCDD is concentrated in adipose tissue, this study provides a possible physiological mechanism for epidemiological studies linking dioxins and diabetes. Experimental study has shown that mice exposure to dioxins, insecticides, or BPA in the womb increases the risk of developing T2DM (Alonso-Magdalena et al. 2011). Animal studies have also shown that some EDCs can directly affect pancreatic cells, adipocytes, and hepatocytes, and induce insulin resistance and hyperinsulinemia. These actions may be related to changes in adiponectin and leptin levels. Animal studies also indicate that some EDCs directly affect cells in the pancreas, adipocytes, and liver, and induce insulin resistance and hyperinsulinemia. These can also be associated with modified levels of adiponectin and leptin. In an adult mice model, Marmugi et al. (2014) have observed the effect of BPA exposure for several months on the hepatic and plasma metabolic markers. The results showed that BPA exposure has a specific impact on glycemia, glucose tolerance as well as cholesterolemia. RT-qPCR on liver mRNA from the same animal shows an overexpression of key genes involved in cholesterol biosynthesis, namely Mvd, Lss Hmgcr, and Sqle.

This is consistent with the hypercholesterolemia in BPA-treated animals. BPA can also induce the expression increase of the sterol regulatory element-binding protein 2 which is a master regulator of hepatic cholesterol biosynthesis. Elevated blood glucose, IGT, jeopardized insulin, reduced glucose-stimulated insulin secretion, and decreased pancreatic insulin contents have been observed in DEHP-exposed mice offspring at postnatal day 60. The offspring of mice exposed to BPA during pregnancy also displayed metabolic disturbances. Decreased insulin sensitivity and increased GSIS were detected within 6 months of life. Notably, men were more adversely affected than women, and lower doses of BPA were more adversely affected than higher doses. Because estrogen in the physiological range protects against diabetes, female offspring may be less affected than males (Farrugia et al. 2021). In the islets of the DEHP-exposed group, the overall DNA methylation levels were increased, while the expression levels of genes involved in the development and function of pancreatic β-cells were down-regulated (Rajesh et al. 2015). The peroxisome proliferator-activated receptors are crucially involved in energy homeostasis and glucose metabolism. The activity of them can be influenced by EDCs. EDCs can also disrupt hormonal regulation by mimicking or blocking normal endocrine functions, which can result in metabolic disorders (Heindel et al. 2015a). The current worldwide increase in metabolic disorders is associated with a substantial increase in the production and exposure of chemicals in our environment (Neel and Sargis 2011). Epidemiological surveys and animal models have shown that the perinatal environment plays a key role in adult metabolic health (Desai et al. 2015). It has been shown that BPA exposure in perinatal rats can result in hyperglycemia, which can lead to insulin resistance in adult male rats (Song et al. 2014). Similarly, BPA exposure during pregnancy was linked to hyperglycemia, hyperinsulinemia, and insulin resistance in F1 adult offspring (Marta García-Arevalo et al. 2014). EDC exposure of the fetus is also possible, and perhaps more likely to cause epigenetic changes, which may be manifested by themselves and passed on to offspring many years later. This triggered a vicious intergenerational cycle of metabolic diseases affecting human health (Bianco-Miotto et al. 2017; Ho et al. 2017; Lee et al. 2019; de Aguiar Greca et al. 2020). Importantly, the metabolic changes triggered by BPA in pregnant mice seemed to resolve after delivery but reappeared later in life. This implies that fetal BPA exposure during gestation has long-term irreversible effects on the risk of metabolic disorders in later adulthood (Farrugia et al. 2021). EDCs induce genome alterations in pregnancy or early life and enchain in a decreased expression of pancreatic/duodenal homeobox 1 transcription factor gene (*PDX1*) associated with an increase in T2DM (Rotondo and Chiarelli 2020), suggesting that in utero exposure to impaired nutrition is a risk for obesity and diabetes progression in adulthood.

Adult ECD Exposure and T2DM

The effects of EDCs on adult organisms or on developing organisms are different. In adult organisms, a high dose of EDCs is required to produce an effect, and the effect disappears when the contact is stopped. In contrast, in developing organisms, exposure to EDCs tends to have long-term effects (Kunysz et al. 2021). It is well known that fetal exposure such as residential exposure of air pollutant concentrations of particulate matter 2.5 μm and nitrogen dioxide (NO_2) results in more harmful effects than adult exposure, one possible reason is the lack of adequate defense and detoxification mechanisms before delivery (Bianco-Miotto et al. 2017). In addition, the levels of cytochrome P450 enzymes which can metabolize environmental drugs and chemicals were lower in the developing fetus than in adults (Cresteil 1998; Hakkola et al. 1998). EDCs can enter the body in several ways. These pathways include digestive tract intake, respiratory tract inhalation, skin contact absorption, and others (Rudel and Perovich 2009). Some EDCs may be even more exposure in newborns and children than in adults because newborns and children require greater consumption of certain specific foods and water. Additionally, the ventilation rates, intestinal absorption, surface area-to-volume ratios, and hand-to-mouth activity are higher in babies and toddlers than in adults (Selevan et al. 2000). Breastfeeding is also a pathway to increase EDC exposure in infants (Grandjean and Jensen 2004). In contrast, adult occupational or workplace and accidental exposure to ECDs is more common. Occupational studies of persistent exposure to EDC have provided the first evidence of diabetogenicity in humans, when PFAS was certificated as a contributing factor to T2DM in samples exposed to these chemicals at work (Lundin et al. 2009). In a population near Washington (WV, USA), although consistent exposure to PFAS-contaminated drinking water was not associated with T2DM (Conway et al. 2016; Karnes et al. 2014), total PFAS concentrations measured in blood samples were associated with T2DM in Swedish (Lind et al. 2014) and American cohorts (Sun et al. 2018; Cardenas et al. 2019). In an American study, dietary intervention has shown to alter the risk of T2DM associated with PFAS exposure (Cardenas et al. 2019). Bisphenols and other non-persistent chemicals were considered to be the strongest associations with diabetogenicity in adults. Several previous case–control studies have associated BPA with an increased risk of T2DM (Li et al 2018; Murphy et al. 2019; Duan et al. 2019), the finding of the Prospective Nurses' Health was also like this (Sun et al. 2014). The effects of BPA on glucose, insulin, and C-peptide have been determined in two small-scale

($n < 25$) intervention studies, suggesting that concentrations deemed safe by US regulators change glucose-stimulated insulin responses in humans (Stahlhut et al. 2018; Hagobian et al. 2017). A previous meta-analysis has estimated EDC exposure and the pooled relative risk of T2DM. It is OR 1.45 (95% CI 1.13–1.87) for BPA and OR 1.48 (95% CI 0.98–2.25) for phthalates (Song et al. 2016). Since then, a case-cohort study in French (Rancière et al. 2019) found that the risk of T2DM associated with measured BPA glucuronide and BPS glucuronide has nearly doubled. This finding increases people's concerns on BPS and other replacements of BPA because they have been widely used in aluminum cans and thermal paper receipts. In addition, exposure to phthalates has associated with increased risk of T2DM in two case–control (Lind et al. 2014; Svensson et al. 2011) and two cohort studies (Sun et al. 2014; Lind et al. 2012). In summary, epidemiological and experimental data have suggested that exposure to polybrominated diphenyl ethers, some non-persistent pesticides and herbicides, parabens, and benzophenones could be associated with T2DM, but more research is needed in these fields.

Transgenerational Effects of EDCs on T2DM

The influences of EDCs on lipogenesis and glucose metabolism may not be limited to directly exposed individuals. Recent data suggest that exposure to EDCs during development not only directly harms the exposed individual, but also harms the individual's offspring and future generations, a process known as transgenerational inheritance (Fig. 1) (Crews et al. 2007; Horan et al. 2017). Numerous animal models have demonstrated a direct causal relationship between EDC exposure in utero and disease outcome, and in some cases the adverse effects can be transmitted to offspring through epigenetic inheritance across generations (Crews et al. 2007; Horan et al. 2017; Wolstenholme et al. 2012). The effects of EDC exposure in pregnant F0 animals have been propagated until at least the F3 generation in several recent studies (Tang-Péronard et al. 2011; Wing and Phelan 2005; Fothergill et al. 2016). When the maternal lineage exposed to EDCs, F0 and F1 animals were also directly exposed to EDCs, and the F2 generation was exposed as germ cells within pregnant F1 animals. The F3 generation was the first generation without direct contact with EDCs. Therefore, the actions observed at F3 and beyond were considered to be transgenerational and permanent (Walker and Ho 2012). The ability to induce permanent epigenetic alterations in germ cells without subsequent long-term exposure suggests a new form of inheritance that may have greater implications for biology, disease etiology, and evolution (Guzylack-Piriou and Ménard 2021). In these models of F0 exposed to EDCs, the persistence of the metabolic abnormalities in the F3 is attributed to epigenetic modifications. The exposure of germ cells is important to take into account when addressing multigenerational effects (Guzylack-Piriou and Ménard 2021). Indeed, the relationship between BPA, tributyltin (TBT), pesticide and phthalate exposures, and increased prevalence of obesity and reproductive disease in animal models has been observed up to the third generation (Kirchner et al. 2010; Manikkam et al. 2013; Maresca et al. 2016). Skinner et al. (2013) clearly demonstrated that exposure to DDT, a mixed hydrocarbon mixture (jet fuel JP-8), and plastic components such as BPA, DEHP, and

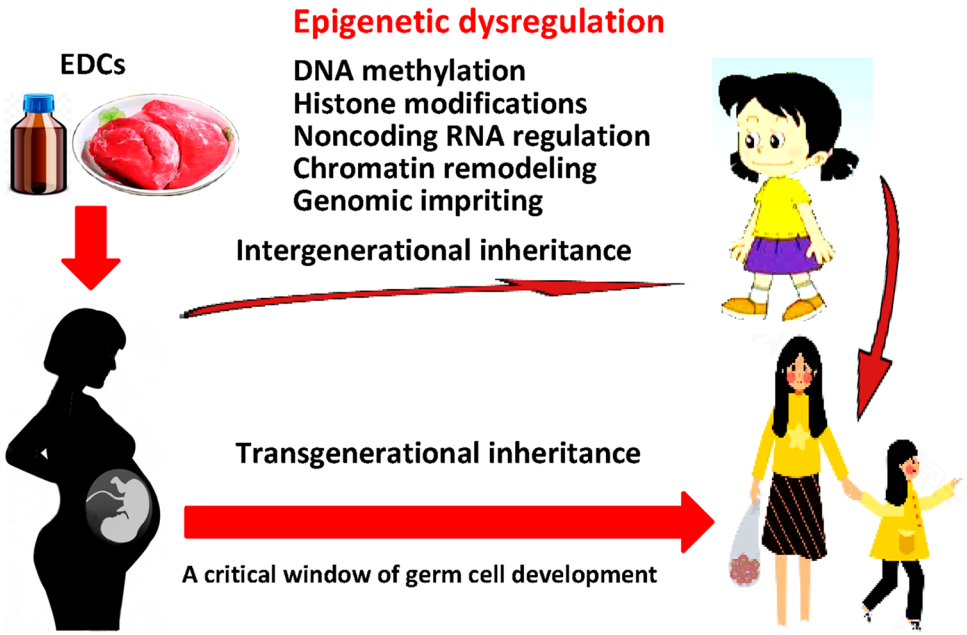

Fig. 1 Transgenerational effects of EDCs on T2DM. Pregnant women exposure to EDCs means direct influence on mother and fetus (intergenerational) and developing primordial germ cells of growing fetus (transgenerational inheritance). EDC exposures in humans begin as early as in the mother's womb (F0). Because some EDCs have been demonstrated to cross the placenta and reach the fetus. During this critical period of early development and growth, intrauterine EDC exposure offspring (F1) has predisposed to increase the risk of metabolic diseases manifested during adulthood

dibutyl phthalate all result in transgenerational obesity in the F3 generation. This effect is related to the epimutations in a network of obesity-related and its complication-related genes. The exact molecular mechanisms of transgenerational effects are not well known, however, a number of EDCs act through nuclear receptors that may be associated with epigenetic changes (Szyf et al. 2015; Radford et al. 2014). Epigenetic modifications may play an important role in the transgenerational effects. Collectively, altered DNA methylation, histone modifications, copy number variants, and microRNA-mediated regulation have all been associated with transgenerational phenotype transmission as a result of exposure to EDCs (Kirchner et al. 2010; Ho and Burggren 2010; Öst and Pospisilik 2015; Guerrero-Bosagna et al. 2014). The transgenerational epigenetic inheritance of changes in glucose homeostasis in animal studies induced by BPA through histone modifications affecting pancreatic and duodenal homeobox 1 (Pdx1) and insulin-like growth factor 2 (IGF2) expression have been demonstrated (Mao et al. 2015; Chang et al. 2016). Exposure to BPA in utero appears to alter epigenetics in the male germ-line and subsequently promotes adult-onset disease in subsequent generations. Fetal exposure to bisphenol A (BPA) has been shown to alter epigenetic modification and result in glucose intolerance in adulthood. Fetal exposure to BPA can also induce epigenetic modification and phenotypic changes in their subsequent offspring. Mao et al. (2015) confirmed that BPA exposure during early life can result in generational transmission of glucose intolerance and β-cell dysfunction in the offspring through male germ-line, which is associated with hypermethylation of Igf2 in islets. The changes of epigenetics in germ cells may contribute to this generational transmission. In addition, the association of perinatal BPA exposure and alteration of hepatic glucokinase (GCK) promoter methylation has also been observed (Ma et al. 2013). These findings further support the potential role of epigenetics in fetal reprogramming by BPA-induced metabolic diseases in adulthood (Ma et al. 2013; Li et al. 2014). These findings suggest that exposure to EDCs could have consequences not only for our own health and for that of our children, but also for the health of the generations to come through environmentally induced epigenetic modifications. Therefore, if we continue to ignore the impact of EDCs on environmental conditions, the sustainability of wildlife and humans will become a conundrum. We cannot currently detect the effects of all EDCs because of EDCs' covert nature, but EDC has become one of the main risk factors that can substantially compromise our environment (Colborn et al. 1993). Therefore, precaution dictates that we cannot wait for exact evidence of harm to humans to take preventive and control actions.

Possible Diabetogenic Mechanisms

The prevalence of T2DM has increased significantly globally at any age over the past few decades. This epidemiological trend in T2DM is consistent with an exponential increase in the production of synthetic chemicals, evidence that prompted us to consider the possibility of a role for EDCs as diabetogenic compounds (Neel and Sargis 2011). Any aspect of endogenous hormonal action can be interfered by EDCs (Kiyama and Wada-Kiyama 2015; Silver et al. 2011; Alonso-Magdalena et al. 2011). In both prospective studies with measurements of exposure in utero and cross-sectional studies in adults, EDCs have been shown to disrupt the peroxisome proliferator-activated, estrogen, and thyroid hormone receptors, among other metabolic signaling pathways (Kahn et al. 2020). PPARγ (PPARG) is a nuclear receptor controlling the expression of genes involved in lipid storage and glucose metabolism and target for obesogenic compounds (Androutsopoulos et al. 2013; Pillai et al. 2014; Janani et al. 2015; Grimaldi et al. 2015). This endocrine disturbance results in an imbalance in the maintenance of key cellular homeostasis, which ultimately increases the risk of unfavorable health conditions (Vandenberg et al. 2012; Xin et al. 2015). Human beings may be exposed to EDCs from a variety of sources, including personal care products, plastic food containers, thermal receipts, medical equipments, and agricultural pesticides. EDC exposure in humans begins as early as in the mother's womb, where several EDCs have been shown to cross the placenta to the fetus (Tang et al. 2020). Developing fetuses and neonates are particularly vulnerable to EDC exposure because the enzymes involved in the xenobiotic biotransformation and elimination of these EDCs are not fully functional during these developmental stages (Choudhary et al. 2003). As a result, excessive accumulation of these EDCs in some target organs and developing tissues such as developing gonads, pancreas, placenta, and brain can lead to their dysfunction (Latini et al. 2004). Furthermore, environmental exposure in early life coincides with extensive epigenetic reprogramming that occurs during early embryogenesis and germ cell specification (Weaver et al. 2009). In the developing fetus, EDCs can alter the maintenance, remodeling, and erasure of epigenetic marks, ultimately leading to increased susceptibility to adult disorders (Schug et al. 2011; Mandy and Nyirenda 2018). The diabetogenic mechanism of EDCs is currently poorly understood. Pancreatic β-cell function might be affected by EDCs through different ways. Several possible diabetogenic mechanisms of EDCs are as follows.

EDCs Disrupt Insulin Production

Diabetogenic EDCs may exert their action on impairing insulin production at the pancreatic β-cell level. EDC actions on pancreatic function can occur through different mechanisms (Street et al. 2018); for examples, TBT reduces β-cell mass and enhances β-cell apoptosis (Zuo et al. 2014); phthalates reduce β-cell insulin content (Lin et al. 2011); BPA impairs insulin secretion (Soriano et al. 2012). (1) In animal models of diabetes, alloxan, a glucose analog and streptozotocin, selectively destroys pancreatic β-cells (Karam et al. 1980). (2) Pyrinuron (Vacor) exposure leads to β-cell destruction and development of type 1 diabetes (Kurita et al. 2009; Fernández-García et al. 2014). (3) A man exposed to high levels of the fungicide chlorothalonil developed diabetic ketoacidosis (Piaggi et al. 2007). (4) Interestingly, some EDCs disrupt β-cell signaling and function, thereby increasing glucose-stimulated insulin secretion (GSIS) in isolated islets, promoting sustained insulin release, and ultimately leading to depletion of intracellular insulin content or promoting β-cell "exhaustion" (Soriano et al. 2012). These EDCs include a PCB mixture (Aroclor 1254) (Alonso-Magdalena et al. 2011), 2,3,7,8-tetrachlorodibenzodioxin (TCDD) (Yau and Mennear 1977), PCBs (Alonso-Magdalena et al. 2011), BPA, and other phenolic compounds such as nonylphenol and octylphenol (Alonso-Magdalena et al. 2005). (5) DDT impairs GSIS and insulin secretion of tolbutamide (Douillet et al. 2013). (6) BPA alters calcium signaling in α-cells (Zuo et al. 2014). (7) TBT promotes hyperglycemia and reduces circulating insulin levels, and it also increases islet apoptosis and reduces cellular proliferation (Bodin et al. 2013). (8) BPA exposure can trigger changes in the β-cell life cycle, with increased apoptosis and decreased proliferation leading to a reduced β-cell mass. These effects are at least partly due to the decreased expression of certain cell cycle activators, such as cyclin D2 (*CCND2*), and the increased expression of some cell cycle inhibitors, such as cyclin-dependent kinase inhibitor 2A (*CDKN2A*). (9) In rat insulinoma cell lines, 48 h of exposure to BPA decreases cell viability, disrupts GSIS, and triggers apoptosis in a dose-dependent manner. BPA activates β-cell apoptotic signaling via the increased expression of pro-apoptotic Bax protein and the reduced expression of anti-apoptotic Bcl-2 (Lin et al. 2013). (10) Makaji et al. (2011) showed that lower doses of BPA (0.1–1.0 μg/L) could increase both basal and GSIS. As GSIS depends on signals generated by β-cell mitochondria, any mitochondrial abnormality could be a potential contributor to metabolic disorders such as T2DM (Maechler and Wollheim 2000). Ultrastructural observation has also confirmed that BPA and other phenolic estrogens induce β-cell mitochondrial swelling with a loss of structural integrity, impair mitochondrial cytochrome C oxidase function, and reduce cytosolic ATP levels in BPA-treated islets (Song et al. 2012). (11) BPA is involved in β-cell damage through interaction with human islet amyloid polypeptide (hIAPP). hIAPP is a 37-residue soluble polypeptide that is produced by β-cells and co-secreted with insulin. hIAPP monomers also have an inherent tendency to misfold, forming β-sheet oligomers that assemble into linear fibrils. The oligomers and fibrils exert cytotoxic effects on pancreatic β-cells by inducing membrane permeabilization and disruption (Brender et al. 2012; Anguiano et al. 2002). The link between hIAPP and T2DM has been demonstrated by studies that IAPP aggregates are detectable in the majority of diabetic patients, and the spatial correlation between IAPP deposition and β-cell mass loss has been well established (Lorenzo et al. 1994; Westermark et al. 2011; Brender et al. 2012). Aggregates of IAPP insert into the β-cell membrane, leading to leakage of cellular contents, ultimately leading to apoptosis. In vitro studies using a rat insulinoma cell line showed that BPA promoted human amylin polypeptide (hIAPP) aggregation and membrane disruption in a dose-dependent manner (Gong et al. 2013). As cell membranes become more permeable, Ca^{2+} ions enter the cell and trigger the production of harmful reactive oxygen species (ROS; Fig. 2).

EDCs Impair Peripheral Insulin Action

Diabetogenic EDCs may also exert their action on disrupting insulin sensitivity in peripheral tissues. EDCs can reduce insulin sensitivity acting on insulin targets, particularly in the liver. In animal models, BPA alters hepatic glucose sensing, impairing glucokinase (GCK)-specific activity (Perreault et al. 2013). (1) EDCs impair insulin signaling or insulin-stimulated glucose handling in different cell lines and organ culture models, including TCDD (Paul et al. 2007; Sargis et al. 2019), tolylfluanid (Xue et al. 2011), inorganic and methylated arsenic species (Rengarajan et al. 2007; Rajesh et al. 2014a), DEHP (Rajesh et al. 2013; Indumathi et al. 2013), and persistent organic pollutants (Chamorro-Garcia et al. 2013). (2) BPA can inhibit insulin-stimulated glucose utilization in 3T3-L1 adipocytes (Lehmann et al. 1995), increase basal and insulin-stimulated glucose uptake in 3T3-F442A cells (Enan et al. 1992), cause hyperinsulinemia, disrupt hepatic insulin signaling, enhance insulin resistance, increase postpartum weight gain, hyperinsulinemia, elevate plasma leptin, triglyceride, and cholesterol, develop IGT, and decrease insulin sensitivity at four months postpartum (Alonso-Magdalena et al. 2011; Farrugia et al. 2021). (3) EDCs disrupt cellular energy processing and promote insulin resistance. For example, in vivo exposure to DEHP downregulates the expression of insulin signaling intermediates in adipocytes (Jayashree et al. 2013); exposure to BPA in rats reduces insulin signaling intermediates in muscle and liver (Han et al. 2003); TCDD reduces glucose uptake in fat and brain (Regnier et al. 2015; Paul et al. 2011); the

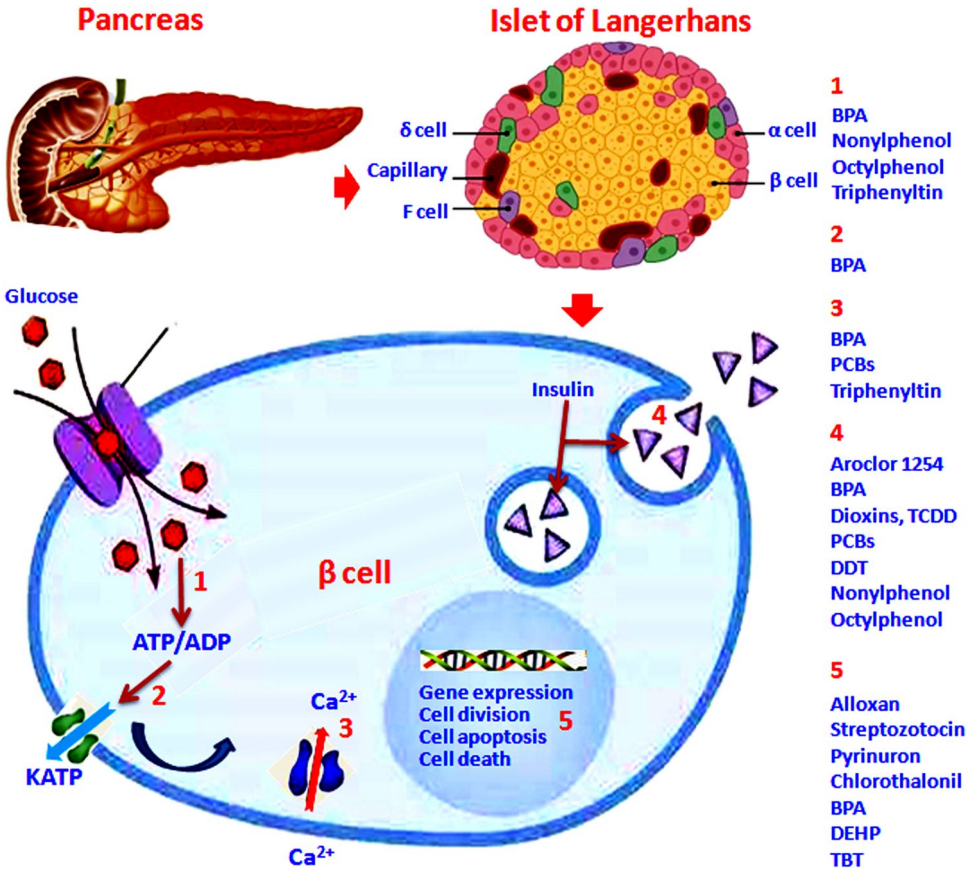

Fig. 2 The possible effect mechanisms of EDCs on pancreatic β cells. Delta (δ) cell: secreting somatostatin; F cell: secreting pancreatic polypeptide; Alpha (α) cell: secreting glucagon; Beta (β) cell: secreting insulin. Circulating glucose enters pancreatic β-cells via the glucose transporter 1. Glucose in β-cells is metabolized in the mitochondria, resulting in an increase in the ATP/ADP ratio; thus causing the membrane ATP-sensitive K^+ channel (KATP) responsible for the resting membrane potential to close. The closure of KATP channels causes cellular depolarization, opens voltage-gated calcium channels, triggers Ca^{2+} signals, induces insulin granule exocytosis, and then increases circulating insulin levels. This secretory pathway can be disrupted by EDCs in different manners: EDCs (1) impair mitochondrial function; (2) block KATP channels after binding ERβ; (3) alter calcium signaling; (4) disrupt insulin secretion; and (5) regulate insulin gene expression via Erα

fungicide to sulfanilide promotes glucose intolerance with concomitant systemic and fat-specific insulin resistance, the latter caused by specific downregulation of insulin receptor substrate-1 (Hill et al. 2009). (4) Long-term exposure to persistent organic pollutants promotes insulin resistance (American Diabetes Association 2011). Likewise, BPA promotes insulin resistance in mice (Nadal et al. 2000), and this effect can be observed with exposure times as short as 8 days (Huang et al. 2015). TBT exposure in mice induces hyperinsulinemia (Lim et al. 2009). (5) BPA enhances insulin resistance in pregnant women, with female offspring exhibiting higher insulin levels, while males exhibit glucose intolerance and systemic insulin resistance (Marta García-Arevalo et al. 2014). Insulin resistance has also been observed in BPA-exposed rats (Wan et al. 2014), and another mouse model similarly exhibits insulin resistance-induced glucose intolerance. However, this effect was only observed at low doses (Hatch et al. 2015). (6) A high-fat diet may increase BPA-induced insulin resistance (Ryan et al. 2010) and enhance GSIS impairment caused by subcutaneous administration of low-dose BPA (Lv et al. 2013). However, in CD-1 mice, developmental exposure to BPA did not alter glucose homeostasis in adult mice fed a normal chow or high-fat diet (Delclos et al. 2014). (7) Exposure to other EDCs during development promotes altered insulin action. For example, exposure to low-dose perfluorooctanoate in middle age increases insulin levels (Rodriguez et al. 2016), while exposure to perfluorooctane sulfonate during pregnancy and early postpartum causes glucose intolerance and insulin resistance (Attina and Trasande 2015). Rats exposed to perfluorooctane sulfonate from gestation day 0 to postpartum day 21 also exhibited glucose intolerance and increased insulin levels (Wang et al. 2010). (8) Development exposure to DEHP resulted in hyperglycemia and concomitant

decreased insulin levels in female rats, while male offspring had elevated insulin levels but normal glucose tolerance (Svensson et al. 2011). In another model, DEHP exposure resulted in glucose intolerance and insulin resistance in offspring, although this model also revealed a central defect in β-cell function (Alonso-Magdalena et al. 2015). (9) Sex-specific effects of DEHP exposure on insulin resistance were also observed in some epidemiological surveys (Lind et al. 2012), but not in others (Kamath and Rajini 2007).

Specific Defects in Intermediary Metabolism of EDCs

With regard to specific defects in intermediary metabolism of EDCs, we remain poorly understood. (1) TCDD reduces the expression of lipoprotein lipase in the 3T3-F442a cell line (Paul et al. 2007), which may promote hypertriglyceridemia. (2) Polybrominated biphenyl ether exposure inhibits adipose glucose oxidation while enhancing isoproterenol-induced lipolysis (Martinelli et al. 2005), possibly increasing circulating free fatty acid levels, which are substrates for hepatic triglyceride synthesis. (3) Perinatal exposure to 4-nonylphenol may induce dyslipidemia, especially increased serum total cholesterol (Yin et al. 2016). (4) Subchronic exposure to malathion results in hepatic metabolic dysfunction, which causes hyperglycemia and increased hepatic gluconeogenesis and glycogenolysis (Turner et al. 2014). (5) Chronic intake of DEHP impairs glucose tolerance with a change in glycolytic intermediates in both liver and muscle, suggesting impaired lactate and glucose handling (Perreault et al. 2013). (6) In a rat model, intrauterine and lactation exposure to BPA decreased hepatic glycogen content at 21 weeks of age, the promoter of hepatic glucokinase was hypermethylated, and the expression of this key enzyme decreased (Wan et al. 2014). (7) In a multigenerational rat model, BPA exposure in the F0 generation promotes glucose intolerance and insulin resistance in the F2 generation, with a concomitant decrease in hepatic glucokinase expression and hypermethylation of the gene promoter (Al-Eryani et al. 2015). (8) BPA exposure in adult mice exhibited reduced hepatic glucokinase activity (Cave et al. 2010), suggesting that disruption of hepatic glucose processing may be a common mode of EDC-promoted metabolic dysfunction. Some diabetogenic EDCs may impair insulin production at the pancreatic β-cell level and disrupt insulin sensitivity in peripheral tissues. (9) Sex-specific effects of DEHP on measures of insulin resistance have been observed in some epidemiological surveys (Lind et al. 2012), but not in others (Kamath and Rajini 2007). These findings suggest that both adult and development exposures to various EDCs have the ability to modulate global insulin action and at the cellular level. (10) BPA also induces oxidative stress in hepatocytes by reducing the activities of antioxidant enzyme superoxide dismutase, glutathione peroxidase, and catalase (Bindhumol et al. 2003), and stimulates lipid accumulation through the upregulation of lipogenic genes, such as sterol regulatory element-binding protein 1 (SREBP1) (Lin et al. 2017; Shimpi et al. 2017). Adult mice sustained exposure to BPA over a period of eight months results in the significant upregulation of genes involved in de novo lipogenesis. These genes include fatty acid synthase (FASN, encoding fatty acid synthase), thyroid hormone-responsive protein (THRSP), syndecan 1 (SDC1), patatin-like phospholipase domain containing 3 (PNPLA3), and sterol regulatory element-binding transcription factor 1 (SREBF1). Moreover, long-term BPA exposure leads to an increase in the key enzymes of de novo cholesterol biosynthesis, including 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) (Farrugia et al. 2021).

Effects of EDCs on Epigenetic Modification

An additional mechanism of EDC action involves the modulation of epigenetic mechanisms through changes in DNA methylation, histone modification, and microRNA expression (Fernandez-Twinn et al. 2019; Cimmino et al. 2020). For instance, BPA can have both short-term and long-term effects with the latter typically occurring through epigenetic mechanisms such as DNA methylation (Mileva et al. 2014). Epigenetics is defined as changes in gene transcription and expression that occur without altering the DNA sequence and result in long-term changes in cellular and biological functions (Jaenisch and Bird 2003). The investigation of epigenetics and its involvement in metabolic diseases is still a young research field, but it is now attracting a lot of attention and growing at a fast pace. Environmental, lifestyle, and dietary factors or gut microbiota can influence the epigenetic programming of parental gametes, fetus and early postnatal development, or through the various periods of life to influence epigenetic programming (Lopomo et al. 2016). The epigenetic states can be transferred through (i) mitotic inheritance to maintain epigenetic changes across cell cycles and/or (ii) meiotic inheritance carried by sperm cell and oocyte to transmit epigenetic changes across generations (Trerotola et al. 2015). The main epigenetic mechanisms include DNA methylation, histone variants/modifications, chromatin-modifying (chromatin remodeling) proteins, and non-coding microRNA-mediated regulation (Fernandez-Twinn et al. 2019). (1) DNA methylation: DNA methylation is the most frequently studied modification because its covalent chemical structure makes it highly stable, and therefore can be quantified in a range of archived tissues and cells. Several studies have demonstrated that environmental disturbances, including assisted reproductive technologies (ART), prenatal famine, and EDCs, are associated with altered global and/or gene-specific DNA methylation patterns (Lucifero et al. 2004; Susiarjo et al. 2013; Tobi et al. 2014). DNA

methylation is a widely studied epigenetic modification that regulates genes with critical roles in a variety of biological processes (Smith and Meissner 2013). This epigenetic modification is associated with gene silencing in regulatory regions. Alterations in DNA methylation patterns can induce aberrant gene expression and appear abnormal phenotypes (Bernal and Jirtle 2010). Finally, DNA methylation is an important regulator of a subset of key genes for fetal and placental development, termed imprinted genes (Kang et al. 2011). In the peripheral blood samples of offspring, Chen et al. (2017) have identified differentially methylated CpGs in 39 genomic regions which were affected by intrauterine exposure to GDM. Methylation at three sites is associated with insulin secretion, while a fourth site is associated with future risk of T2DM. The study conducted by Declerck et al. (2017) showed that prenatal EDC exposure was associated with a differential DNA methylation profile in children carrying the *PON1* 192R-allele compared to children with the *PON1* 192QQ genotype and unexposed children. Differentially methylated genes were enriched in several neuroendocrine signaling pathways including T2DM signaling. These findings suggest that DNA methylation may be an underlying mechanism explaining an adverse cardio-metabolic health profile in children carrying the *PON1* 192R-allele and prenatally exposed to EDCs. Pyrosequencing showed that the G protein-coupled receptor 39 (GPR39) DNA methylation was reduced in prenatally pesticide exposed R-allele carriers. GPR39 is obestatin receptor belonging to the ghrelin receptor family. It was involved in regulation of appetite and glucose homeostasis (Zhang et al. 2005; Verhulst et al. 2011; Declerck et al. 2017). Interestingly, some of the mediator marks linked to specific genes were also changed in prenatally pesticide exposed children. For example, fatty acid-binding protein 4 (*FABP4*) encodes for a member of the fatty acid-binding protein family regulating lipid trafficking, signaling, inflammation, and metabolism. Different studies have demonstrated the role of this protein in obesity, T2DM, and atherosclerosis development (Furuhashi et al. 2014; Wu et al. 2014; Hotamisligil and Bernlohr 2015). In addition to causing changes in DNA methylation patterns, EDC exposure has been shown to disrupt other parameters of epigenome programming, including histone modification pattern. Several different modifications can occur within the highly basic histone amino (N)-terminal tail region (Bannister and Kouzarides 2011). These modifications can affect the interaction of these (N)-terminal tails between subunits of the same nucleosome or between subunits of adjacent nucleosomes. These modifications can also recruit and interact with chromatin-remodeling enzymes that alter the overall structure and conformation of chromatin. (2) Histone modification: In addition to causing changes in DNA methylation patterns, EDC exposure has been shown to disrupt other parameters of epigenome programming, including histone modification pattern. Several different modifications can occur within the highly basic histone amino (N)-terminal tail region (Bannister and Kouzarides 2011). These modifications can affect the interaction of these (N)-terminal tails between subunits of the same nucleosome or between subunits of adjacent nucleosomes. These modifications can also recruit and interact with chromatin-remodeling enzymes that alter the overall structure and conformation of chromatin. In this way, histone modifications can regulate gene transcription by affecting the accessibility of promoter sequences to transcriptional complexes required to initiate gene expression. Chang et al. (2016) also found that maternal exposure to BPA reduces pancreatic β-cell mass at birth by reducing PDX1 + progenitors during fetal development through altering the histone modifications of Pdx1 [histones H3 and H4 deacetylation, along with demethylation of histone 3 lysine 4 (H3K4) and methylation of histone 3 lysine 9 (H3K9)], which can be propagated to later life and increase the susceptibility to glucose intolerance. (3) microRNA-mediated regulation: More recently, a class of small non-coding RNAs called microRNAs (miRNAs) are emerging as key regulators of metabolic abnormalities (La Sala et al. 2020). miRNAs are short non-coding RNA sequences of 18 to 25 nucleotides in length that are capable of regulating gene expression through gene silencing and post-transcriptional changes (Pasquinelli 2012). Since they were discovered in 1993, miRNAs are present in all eukaryotic cells conserved across species. miRNAs regulate gene expression by inducing mRNA cleavage or by inhibiting protein translation, and by binding to complementary sequences in the 30-untranslated regions (30UTRs) of target messenger RNAs (mRNAs), thereby reducing their stability and translation efficiency (Sluijter and Pasterkamp 2017). Dysregulation of miRNA expression has been shown to regulate pathological pathways involved in the development of various diseases (Vishnoi and Rani 2017). Accumulating evidence supports intra- and extracellular miRNAs as determinants of crosstalk between adipose tissue, liver, skeletal muscle, and other organs, triggering paracrine communication between different tissues (La Sala et al. 2020). More than 2500 mature miRNAs have been found in the human genome (Kozomara et al. 2019). More than 60% of protein-coding genes in the human genome are reported to be targeted by miRNAs (Akhtar et al. 2016), with a single miRNA capable of targeting and regulating thousands of mRNAs (Ghorai and Ghosh 2014). Thus, miRNAs are considered key gene regulators in a variety of biological processes, including adipocyte proliferation and differentiation, and have been associated with insulin resistance in obese individuals (Cruz et al. 2017). In a recent study, Wei et al. (2020) showed that di(2-ethylhexyl) phthalate (DEHP) inhibits miR-17 to disrupt the Keap1-Nrf2 redox system and activate oxidative stress-responsive Txnip in skeletal muscle. Oxidative stress upregulates miR-200a,

which directly targets the 3'UTR of Insr and Irs1, leading to impaired insulin signaling and insulin-dependent glucose uptake in skeletal muscle, ultimately promoting the development of insulin resistance. Adeno-associated virus 9 (AAV9)-induced overexpression of miR-17 and lentivirus-mediated silencing of miR-200a in skeletal muscle ameliorates systemic insulin resistance in mice exposed to DEHP. These findings suggest that the miR-17/Keap1-Nrf2/miR-200a axis contributes to DEHP-induced insulin resistance. miR-17 is a positive regulator, while miR-200a is a negative regulator of insulin signaling in skeletal muscle, and both miRNAs have potential therapeutic targets for the prevention and treatment of insulin resistance or T2DM. In addition, several polymorphisms in the melatonin receptor 1B (*MTNR1B*) are associated with T2DM, fasting glucose concentration, and insulin secretion (Mussig et al. 2010; Nagorny and Lyssenko 2012; Karamitri et al. 2013). The complex interplay between genetic or polygenic susceptibility, adverse fetal environment, and the environmental impact of EDCs may lead to the activation or inactivation of genes through epigenetic mechanisms, enabling adaptation (in some degree) to various environmental situations, but sometimes bringing about the development of various diseases. Given that some epigenetic changes are reversible, the identified epigenetic marks could be important diagnostic measures, therapeutic targets, and potential prognostic tools.

Conclusions and Future Outlook

Since the probable exposure-outcome associations of EDCs and T2DM were identified, there has been an increase in studies in humans of exposure to EDCs and a deepened understanding of their effects on T2DM. For example, the relationship between exposure to PFAS and phthalates in adulthood and child and adult obesity, IGT and GDM has been observed; the association between exposure to PFAS, phthalates as well as bisphenols and adult diabetes has also been noticed (Kahn et al. 2020). EDCs have been now recognized as serious and urgent threats to public health, potentially emerging as one of the leading environmental risks globally. There has been increasing recognition that the risk of T2DM can be affected by EDC exposure, especially prenatal, neonatal, and childhood EDC exposures. Exposure to EDCs at these developmental window periods may alter the maternal gestational milieu and result in an increased risk of offspring's endocrinopathy and metabolic diseases in adulthood. Although the profound effects of EDCs on adipocyte physiology and glucose metabolism have been demonstrated in previous experimental animal models, evidence in human beings remains scant and data are often conflicting. It is difficult to conduct studies with experimental animals using different EDCs and to determine the underlying alterations observed in human studies. Furthermore, it seems more difficult to demonstrate a direct effect of EDCs in humans (He et al. 2020). Therefore, it is difficult to draw a firm conclusion from these limited evidences and inconsistent results. The reasons for these differences are complex and may be the results of different factors, including confounding factors, the complex mixtures of exposures and their interrelationships, the intrinsic characteristics of each EDC, the variability in exposure distribution of EDCs in the environment and timing across studies, the cross-sectional designs of many studies, and the imprecision of exposure assessment methods, especially for chemicals with short half-lives (Kahn et al. 2020), developmental time windows of exposure and concomitant exposure to a mixture of chemicals that may synergistic effects in mixtures of chemicals, known as the cocktail effect phenomenon (Le Magueresse-Battistoni et al. 2017), the type and dose of the chemical, the timing of exposure, the metabolic route (Pinos et al. 2021), differences in maternal age, BMI, probe set, race and ethnicity, socioeconomic status, and educational background of the studies, and variability in BPA exposure and metabolism between individuals and populations (Farrugia et al. 2021). This complexity makes it difficult to develop robust epidemiological models to study the mechanism of action of EDCs in humans and to understand the actual clinical impact of each EDC. In addition, the major publications in this field involve cross-sectional or case–control studies. Longitudinal studies are still very limited. Therefore, further studies are still needed to elaborate on the effects of EDCs and other synthetic chemicals on human T2DM with greater precision, and more research is also necessary to confirm or strengthen data derived from experimental models and cross-sectional studies, and improve understanding of whether repeated exposures over time or just short-term exposures to EDCs during critical windows of development are related to T2DM. Metabolomic technologies hold promise in the identification of a broad array of emerging and novel exposures. The application of exposomic methods can yield more integrated views about combined effects of multiple exposures to a particular phenotype (Pinos et al. 2021), and offer mechanistic insights and opportunities to develop intermediate markers that could reliably predict disease endpoints and aggregate effects of multiple interacting exposures. Genomics and related tools can carefully examine gene-exposure interactions and their influence on the health outcomes of exposure to ECDs (Engel et al. 2016). Additionally, larger sample sizes are also needed to sufficiently power interaction testing across chemical mixtures. Although systematic evaluation is needed of the probability and strength of these exposure-outcome associations, the growing evidence supports urgent action to reduce exposure to EDCs. As Bradford Hill described in his landmark lecture on causality, actions—in this case, to reduce exposure to

EDCs—require consideration of the evidence and the stakes involved in the decision (Hill 1965; Kahn et al. 2020). In many cases, alternative manufacturing practices can be applied to mitigate exposure to EDCs. Although there are actions that individuals can take to reduce their exposure, the definitive way to make a difference on a population level is through regulation. Regulation policies can reduce exposure, prevent disease, and produce economic benefits that might even outweigh the costs of safer alternatives (Kahn et al. 2020).

Author Contributions J-YL performed the literature search and review, wrote the manuscript, and ideated and produced the figure and table. R-XY conceived and designed the paper, ideated and produced the figure and table, and critically revised the manuscript. Both authors read and approved the final manuscript.

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Data Availability All data and citations used within this review are available online.

Declarations

Conflict of interest The authors declared that they have no conflict interest.

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