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RESEARCH ARTICLE

Insulin Resistance in Children and the role of Endocrine-Disrupting Chemicals: Taking Stock of the Situation

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ABSTRACT:
The prevalence of non-communicable diseases, of which insulin resistance is a major constituent, among the pediatric population is exponentially increasing worldwide; this is causing a significant health burden, making understanding the basis of this phenomenon an issue of primary importance. During the last decades, we also observed that exposure to endocrine-disrupting chemicals is becoming more and more common; this has led researchers to investigate the mechanism of action and define the role of those substances in interfering with human metabolism and hormonal balance, especially at a young age. We reviewed the literature on prospective, epidemiological, and cross-sectional studies that have shown a link between exposure to pesticides, polychlorinated biphenyls, bisphenol A, phthalates, aromatic polycyclic hydrocarbons, or dioxins and insulin resistance; the strength of the associations varies between the substances and human biomonitoring studies have helped in defining the role of these chemicals. The number of prospective studies in children and even in adults is still low and heterogenous, still, evidence that Endocrine disruptors might be involved in the development of insulin resistance and related diseases is accumulating. This review aims to analyze the latest findings linking exposure to endocrine-disrupting chemicals with insulin resistance in children with the perspective of taking a cue for conducting new studies and identifying the most concerning Endocrine disruptors exposures, in order to guide future risk assessment and policy action aimed to limit the negative consequences of endocrine disrupting chemical exposure.

1. INTRODUCTION

Endocrine-disrupting chemicals are a class of exogenous chemicals able to interfere with normal endocrine physiology by influencing hormone metabolism in terms of synthesis, actions, and homeostasis. Endocrine-disrupting chemicals exposure is almost inevitable since their presence is practically ubiquitous in products from industrial processes, or in food [1](such as soy, legumes, other plant-based products, etc.) and its containers; they can be easily found in air, water, soil, household and personal care products, toys, construction materials, even medical devices (drugs, sanitizers, furniture and so on). Most of these substances can cross the placenta and the evidence of their role in the developmental origin of diseases such as obesity and diabetes are more and more solid as our knowledge about their mechanism of action progresses. Plenty of epidemiological data suggests the significant role of in-utero exposure to Endocrine-disrupting chemicals in determining the rise in diabetes, cancer, and infertility that has been observed in the past decades.[2–5] The number of epidemiological studies and animal- and cell-based models proving that exposure to endocrine-disrupting chemicals, both in utero and during one's lifetime, can have effects on human health gets larger and larger every day. Endocrine-disrupting chemicals may affect the organism by means of direct interaction with hormonal receptors or by influencing enzymatic stages of steroidogenesis and neurotransmitter synthesis; they might also affect epigenetic regulation of endocrine and nervous pathways.[6,7] Infants and children are the most susceptible population because of the differences in anatomy, diet, habits, and metabolism kinetics: a significant example might be the lower levels of cytochrome P450 enzymes [8,9]. Our purpose is to analyze the latest findings linking exposure to endocrine-disrupting chemicals with insulin resistance in children with the perspective of focusing on which type of studies are still needed in order to gain a better understanding of Endocrine-disrupting chemicals' actions and to identify the most concerning exposures, in order to guide future risk assessment and policy action aimed to limit the negative consequences of endocrine disrupting chemical exposure.

2. ENDOCRINE DISRUPTORS STUDIES: DEFINITION, LIMITATIONS, PERSPECTIVES

Since the term "endocrine disruptors" was first used, numerous definitions have been proposed: using the major components of the International Program on Chemical Safety and World Health Organization/ World Health Organization and the UN Environment Program / and World Health Organization definition of an Endocrine-disrupting chemical [10], identifying a compound as an Endocrine-disrupting chemical, requires an appraisal of the following:

- Evidence of an (adverse) effect (taking in mind that adverse effects might be reversible; there can be a continuum from "initiating events" to "apical effects" induced by the chemical, and that there remains a debate about what should be considered "adverse" outcomes).[11–13]
- Evidence of endocrine-disrupting activity (considering that endocrine-disrupting activity includes disruption of hormone binding, synthesis, secretion, transport, and metabolism).
- Evidence of a plausible link between the observed adverse effect and the endocrine-disrupting activity.

The presence of Endocrine-disrupting chemicals can be assessed in several human biological samples by means of both gas chromatography and liquid chromatography-mass spectrometry (MS)-based methods; The characteristic of those analytical methods for Endocrine-disrupting chemicals' detection are listed in table 1. When talking about Endocrine-disrupting chemicals it is important to notice the methodological limitations in assessing consolidated and universally effective conclusions and to focus on longitudinal studies (since exposure to Endocrine-disrupting chemicals may vary over time) considering, at the same time, the several different types of exposure. Another main goal is to identify within the population the more exposed or more sensitive subgroups (by sex, ethnicity, etc.); It must be considered, also, that in real life the subjects are more likely to find not only the individual Endocrine-disrupting chemical but mixtures of substances, therefore to fully understand the potential risks is mandatory to study the complex mixtures to which the population is exposed; to reach this purpose an isomer-specific approach seems to be a solution.[14] It is also relevant to standardize laboratory and statistical analysis methodologies in order to increase the accuracy of the evaluation, not only of the presence and concentration of Endocrine-disrupting chemicals but also of their biological action through the modern techniques of the so-called "omics" (proteomics, metabolomics, transcriptomics, etc.) trying to converge the data of the various "omics" with those of genomics to reach the desirable personalized medicine through deepened knowledge of epigenetic interference. Currently available omics

technologies allow us to measure changes caused by Endocrine-disrupting chemicals by monitoring global gene expression (transcriptomics), protein (proteomics), metabolism (metabolomics), and microbe (microbiome) levels [15,16]

The European Commission's Horizon 2020 Research and Innovation Program has granted projects gathered in the European Cluster to Improve the Identification of Endocrine Disruptors (EURION)[17]. This latter received funds up to 50 million euros from the European Commission: the purpose is to screen methods to identify Endocrine-disrupting chemicals; each project focuses on the development of a test method to identify Endocrine-disrupting chemicals outcomes, using an "adverse outcome pathway" framework. The goal is to define new tests, including in silico predictive models and high throughput screening, in vitro models, experiments in rodents and zebrafish, and finally humans.

Techniques and their main features:	**Limitations**
Gas chromatography-MS (Used for identifying organic pollutants, biological matrices and environmental screening; possibility to quanitficate even the small amounts)	- Required expertice - Derivatization treatment needed for non-volatile compounds and polar molecules - Time consuming
High-resolution gas chromatography-negative chemical ionization-MS (accuracy, and high sensitivity, possibility to Identification of compounds with functional groups- ex. phenolic compounds- or with complex chemical components)	- Complex and expensive - Derivatization treatment needed - Time consuming
Liquid chromatography (LC) methods - **High-pressure LC** - **-LC-MS** - **LC-high resolution MS** (reproducible, selective, requires only small samples can Identify a multi-class EDCs)	- Expensive - Expertise needed for analysis - Time consuming - Byproducts

Table 1. Main analytical methods for Endocrine-disrupting chemicals' detection and their limitations[18–20]

2.1 MAIN ENDOCRINE DISRUPTORS

2.1.1 Bisphenol A and Phthalates

Bisphenol A and phthalates are the most studied Endocrine-disrupting chemicals with potential effects on human health, although they're considered "non-persistent" chemicals, they can be easily found in the environment and food due to the persistent release during production processes; Human exposure to these Endocrine-disrupting chemicals may occur through the ingestion of food, inhalation of air and dust in indoor environments, and contact of dust and articles with human mucous membranes and skin. Bisphenol A and phthalates can change the expression of noncoding RNAs, affecting microRNA expression in placental, Sertoli, and cancer cell lines.[21]

Since the 1950s Bisphenol A resins (fig.1) are used as protective coatings for food and drinks cans, as well as for tanks for drinking water storage. Bisphenol A is also used in everyday life supplies such as paints, medical devices, printing inks, and flame retardants. The European Commission Regulation defined that Bisphenol A cannot be used in the manufacture of infant feeding bottles and drinking cups or bottles on the basis of the precautionary principle. [22] Bisphenol A was demonstrated to interact with several nuclear hormone receptor (NHRs), such as the estrogen receptor (ER) (agonist), the orphan receptor human estrogen-related receptor gamma, the androgen receptor (AR), the glucocorticoid (GR), and the PPARγ, and to interfere with the thyroid axis cting as antagonist of thyroid hormone receptor (ThR). [23] The strength with which Bisphenol A binds ER is weaker than that of endogenous estrogen; however, the number of receptors and signaling pathways that may be activated/ influenced by Bisphenol A may explain estrogenic effects even at very low doses. [24] Bisphenol A exposure seems to lead to decreased circulating levels of androstenedione and free testosterone as well as increased levels of sex-hormone binding globulin [25–27]. It is also known to interact with cell surface membrane receptors, (ex. the G-protein coupled estrogen receptor) [23] reducing the proteasome-mediated degradation of ERβ[28]. Lastly, it seems that this compound also affects pancreatic β-cell

inducing a rapid closure of ATP-sensitive K+ channels, a potentiation of glucose-dependent Ca2+ signals, and the release of insulin via binding at extranuclear ERβ [29]. It can also act by increasing glucose-induced insulin biosynthesis after binding to extranuclear ERα [30]. In some consumer products, Bisphenol A is substituted by bisphenol F and bisphenol S , nevertheless, those compounds showed a similar or even greater estrogenic activity [31].

Phthalates (fig.2) are the esters of 1,2-di benzene dicarboxylic acid Phthalates are a class of Endocrine-disrupting chemicals used in a variety of consumer products to increase the flexibility and other properties of plastic materials. These substances can be found in toys, upholstery, clothing, adhesives, food packaging, personal care items, and medical devices. The European Commission Regulation authorized the use of phthalates in plastic food contact material, but in 2018 it was specified that they shall not be used in toys or childcare articles, individually or in any combination if their concentration exceeds 0.1% (by weight) of the plasticized material[22]. Considering the migration of phthalates from plastic to food, in 2019 the European Food Safety Authority defined specific tolerable daily intake values for phthalates. [32] Phthalate particles in dust might be a big issue for children given their habit to touch and mouthing things.

Phthalate exposure occurs through ingestion, inhalation, or dermal absorption [33–36]. It has been shown this substance can cross the placenta, resulting in fetus [37]. After ingestion or inhalation, the phthalates are rapidly hydrolyzed to their respective mono-ester metabolites [38]. Low molecular weight phthalates (di-ethyl phthalate, di-n-butyl phthalate, and di-iso-butyl phthalate) are excreted in the urine as glucuronide or sulfate-conjugated hydrolytic monoesters, while mono-2-ethylhexyl phthalate, the hydrolytic metabolite of di-2-ethylhexyl phthalate undergoes additional enzymatic oxidation before being conjugated and only then excreted. Even though phthalates do not persist in the body and have short biological half-lives (<24h) repeated exposure might result in persistent presence of this Endocrine-disrupting chemicals in the organism.

Phthalate exposure is assessed using urine biospecimens since phthalates are predominately excreted in the urine and blood levels, which are considerably lower, may be subject to exogenous contamination during sample collection, storage, or processing [39]. Accurate phthalate exposure assessment necessitates the collection and analysis of multiple urine samples[40]. Phthalates may interfere with the action or metabolism of androgens, thyroid hormones, and glucocorticoids since they interact with AR, eliciting anti-androgenic effects, therefore decreasing the expression of the mineralocorticoid receptor and inappropriately demethylating MR DNA in testes [40,41] ; it has also been shown an interaction with the PPARs and the AhR [42].

2.1.2. Perfluoroalkyl Substances

Perfluoroalkyl substances (PFAS) are a class of man-made fluorinated substances (fig. 3) present in stain/water resistant coatings for non-stick cookware, textiles, fire-fighting foam, food container coatings, floor polish, and industrial surfactants [43]; those Endocrine-disrupting chemicals are found in a wide range of consumer products such as fast food packaging, paints, personal care products containers, photographic processes supplies. PFA's main characteristic is the presence of multiple fluorine atoms attached to an alkyl chain; due to the strong C-F chemical bond, those substances are extremely resistant to thermal, chemical, and biological degradation, which results in bioaccumulation and persistence in human tissues and environment for an unknown amount of time and may take years to leave the body[44]. PFAS have long biological half-lives in humans, ranging from 3.8 to 7.3 years, and some PFAS (perfluorooctanoic acid, perfluorooctane sulfonate, perfluorononanoic acid, and perfluorohexane sulfonate) are known for their ability to cross the placenta [2,3,5,45].

2.1.3. Trichlosan

Triclosan is a chlorinated aromatic compound endowed with functional groups representative of both ethers and phenols (Figure 4). This compound has antimicrobial properties since it disrupts bacterial cell membrane integrity and lipid synthesis and therefore is used in a large variety of consumer products especially those involved in cleaning and personal care. Exposure is mainly through oral and dermal routes [46]. Triclosan is classified as a not persistent compound since it has a biological half-life of less than 24 h and is predominately excreted in the urine as a glucuronide or sulfate conjugate [47]. Human exposure to Triclosan is measured using urine biospecimens for the same reasons that bisphenol A and phthalates are measured by these means [38]. Finally, biomonitoring studies indicate nearly universal triclosan exposure among pregnant women and children.[3,48,49]

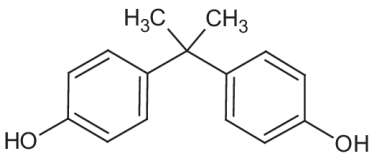

FIG. 1 Bisphenol A

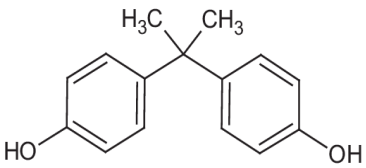

FIG. 2 Pthalates

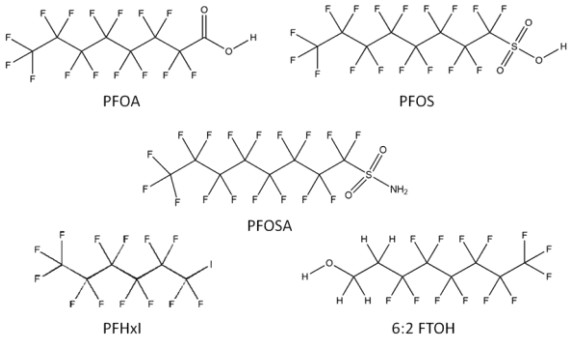

FIG.3 some PFAS

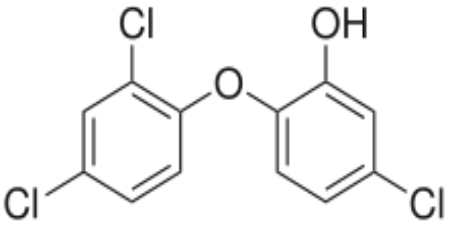

FIG.4 Trichlosan

3. PEDIATRIC POPULATION SUSCEPTIBILITY BASIS

Infants and children have multiple differences from adults and that might significantly influence their response to Endocrine-disrupting chemicals in terms of higher exposure and, therefore, more evident negative outcomes; this mismatch is due to differences primarily in physiology and anatomy, but also in pharmacokinetics, diet, and behavior.[8,9,50] Children are also more sensitive to the effects of Endocrine-disrupting chemicals than adults: the different kinetics [9]of environmental chemical metabolites often result in higher concentrations of Endocrine-disrupting chemicals (in circulating blood or tissues) for an administered dose. During early development, many factors are programmed, most of them being sensitive to disruption by means of Endocrine-disrupting chemicals, resulting in an increased risk of developing childhood diseases; this means that early-life exposure to Endocrine-disrupting chemicals can result in promoting childhood obesity, liver dysfunction, and cardiometabolic impairment by perturbing the neuroendocrine system. To be more specific, some examples of the characteristics that make the pediatric population more prone to Endocrine-disrupting chemicals effect are:

- The amount of water, food, and air introduced into children's organisms in proportion to body surface area outclasses the quantity needed in adults.
- The immaturity of children's blood–brain barrier makes them more sensitive to neurological damage.
- Infants' skin is more water-permeable.
- Children spend more time inside buildings or settings rich in sources of Endocrine-disrupting chemicals, such as construction materials but also tools of everyday use and toys; in addition, infants' tendency to mouthing increases their exposure to Endocrine-disrupting chemicals.
- During developmental age, biological systems and organs are in different stages of maturity and functionality, and this makes the detoxification system less efficient.

The above-listed perturbations (which appear to be more significant in children)[51] may lead to an altered glucose metabolism by means of metabolic changes following one another in a cascade; this consequently increases pancreatic insulin secretion and resistance, resulting in a significantly reduced tissue response to insulin-mediated cellular actions, reducing the effectiveness of insulin in stimulating glucose usage and suppressing hepatic glucose output. In addition, it accounts for interfering with insulin function on the metabolism of lipids and protein; it is to be taken into consideration that the gene expression and function of the vascular endothelium are also affected.

4. DEFINITION OF INSULIN RESISTANCE

Insulin resistance is defined as the decreased tissue response to insulin-mediated cellular actions and is the inverse of insulin sensitivity. As generally applied, the term "insulin resistance" refers to whole-body reduced glucose uptake in response to physiological insulin levels and its consequent effects on glucose and insulin metabolism. Euglycemic hyperinsulinemic clamp studies have shown that insulin resistance is determined primarily by the response of skeletal muscle (over 75% of infused glucose is taken up by muscle compared with 2–3% by adipose tissue).[5253]

Obesity is the most prevalent pathophysiological cause of insulin resistance. Insulin sensitivity is inversely associated with body mass index and body fat percentage, therefore obese children seem to have lower insulin sensitivity than their normal-weight peers. [54] [55] Increased abdominal adipose tissue in the overweighted pediatric population is linked with lower insulin sensitivity and higher acute insulin response.[56] Some studies displayed that ectopic fat deposition in obese adolescents is also associated with decreased peripheral insulin sensitivity. [57] Studies using the clamp methodology demonstrate that non-alcoholic fat liver disease is related to hepatic and insulin resistance.[58] The relation between insulin sensitivity and non-alcoholic fat liver disease seems to be, at least partially, driven by abdominal fat.[59] The relationship between lifestyle factors, i.e. nutrition and physical activity, and insulin sensitivity is poorly defined in children. Increased caloric intake leading to obesity, rather than the dietary macronutrient composition, is associated with insulin resistance and hyperinsulinemia.[60] Adolescent girls with polycystic ovary syndrome can have severe insulin resistance with increased risk for impaired glucose tolerance and type 2 diabetes, the impairment in insulin sensitivity seems to be more pronounced in obese than lean polycystic ovarian syndrome girls. [61,62]

Studies conducted on adult twins show that approximately half of the variance in insulin sensitivity and secretion can be attributed to genetic factors,[63,64] nevertheless insulin resistance is a complex condition influenced not only by genetic factors; several environmental factors play a key role in its etiology too and among them, Endocrine disrupting chemicals are in the leading group.[65]

5. INVESTIGATED MECHANISMS

Metabolic disorders such as insulin resistance and childhood obesity are becoming predominant public health problems worldwide due to their increasing incidence and negative consequences on health that begin in childhood but manifest also in adulthood. The Parma Consensus Already in 2015 highlighted how Endocrine-disrupting chemicals disrupt metabolic systems during critical periods of development with an impact on non-communicable diseases such as obesity, diabetes and metabolic syndrome.[66] The major mechanism through which Endocrine-disrupting chemicals affect insulin resistance are schemed in FIG.2. Some Endocrine-disrupting chemicals are well known "metabolic disruptors" because they can disrupt homeostasis and reward mechanisms increasing individual sensitivity.[67–69] Endocrine-disrupting chemicals seem to lead to insulin resistance both through a mechanism that induces obesity and by direct action on B-cell physiology. [70]PPARγ plays a role in the regulation of adipogenesis [71] and any Endocrine-disrupting chemical acting as agonist on this receptor results in promoting adipogenesis increasing both the number and the mass of adipose tissue cells [9,266]. Endocrine-disrupting chemicals contribute to the etiology of obesity and IR in several ways including the promotion of the signal of adipose cell lines, PPARγ activation, the promotion of fat deposition and potential epigenetic mechanisms; moreover, many Endocrine-disrupting chemicals can promote interactions and changes in the endocrine activity of adipose tissue itself, and the homeostatic systems related, by accumulating in the adipose tissue [72–75] . Endocrine-disrupting chemicals affecting β-cells or disrupting their function were defined "diabetogen" and "diabetogenic hypothesis" suggested that every Endocrine-disrupting chemicals circulating in plasma able to produce insulin resistance, independently of its obesogenic potential and its accumulation in adipocytes, may be considered a risk factor for metabolic syndrome and Type 1 Diabetes.[76] Human studies evaluating Endocrine-disrupting chemicals effects on the pathogenesis of type 1 diabetes are controversial therefore this field requires further studies due to the increasing incidence of IR and diabetes worldwide.[77] Bisphenol A is probably the most investigated obesogenic substance and it seems to promote adipogenesis through Endocrine-disrupting chemicals.[78–81] Acute treatment with Bisphenol A causes temporary hyperinsulinemia, whereas long-term exposure suppresses adiponectin release and gets worse IR, favoring the development of obesity-related syndromes and diabetes. The hyperinsulinemia is attributed to the very rapid closure of ATP-sensitive K+ channels, the potentiation of glucose-stimulated Calcium mediated signals, and the release of insulin via binding at extranuclear ER.[82,83] Bisphenol A exposure during the prenatal period was

associated with increased blood pressure in girls and blood glucose in boys.[84] Adolescents with polycystic ovarian syndrome seem to have significantly higher Bisphenol A levels when compared with healthy ones.[85] A systematic review and meta-analysis concluded that phthalates and their metabolites concentrations were significantly associated with BMI, and waist circumference, affecting levels of low-density lipoprotein cholesterol, triglyceride, and glycemia. Therefore, the reduction of phthalates exposure should be performed since it seems to be a significant prevention strategy [86,87]. Among PFASs, perfluorooctanoic acid and Perfluorooctane sulfonate exposure increased the risk of cardiovascular diseases more than other types of PFASs.[88] Positive associations were found between maternal serum PFASs concentrations and child overweight/obesity[89]. Prenatal exposure to high PFASs levels alters lipid profiles in newborns increasing the risk for islet autoimmunity and diabetes. Moreover, the interaction between human leukocyte antigens risk genotype and prenatal PFASs exposure was suggested to play a role in altered lipid profiles in newborns at a risk of developing diabetes.[90] Several scientific pieces of evidence suggest that exposure to Endocrine-disrupting chemicals during prenatal life, early infancy, and pubertal times, might cause an abnormal distribution of adipose tissue leading to metabolic complications; more conclusive data on the relationship between Endocrine-disrupting chemicals and metabolism are needed: EURION project [17]includes three projects focused on integrated approaches for the testing and assessment of metabolism disrupting chemicals: EDCMET[91], GOLIATH[92], and OBERON[93].

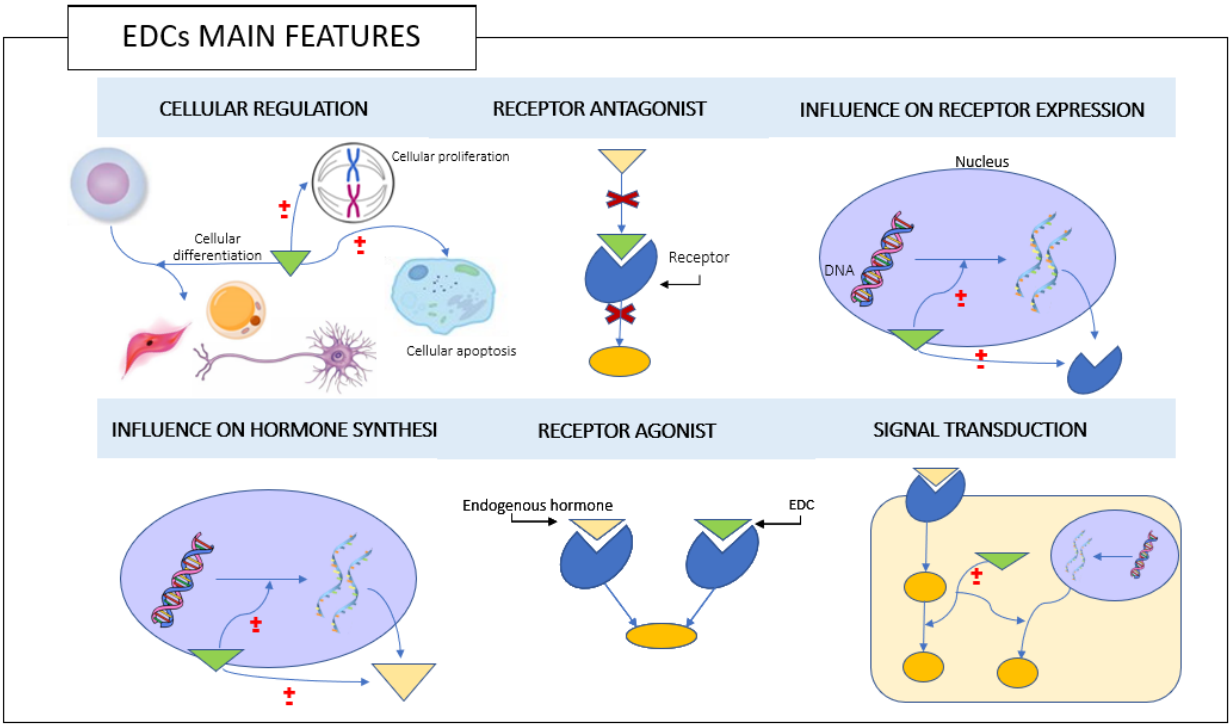

FIG.2 The ± symbol indicates the ability of Endocrine-disrupting chemicals to increase or decrease processes and effects.

5.1 Basis of Endocrine-disrupting chemicals-related insulin resistance

Since adipocytes have a primary role in the maintenance of metabolic balance, especially glucose and triglyceride uptake from the bloodstream in response to insulin, the dysfunction of adipocytes contributes to insulin resistance. Several Endocrine-disrupting chemicals have been related to the development of obesity. Grün and Blumberg used the term "obesogenic" related to Endocrine-disrupting chemicals for the first time in 2006 [94]Adipocytes affected by obesogens have shown to have impaired glucose uptake and insulin signaling, reduced expression of brown adipocyte marker genes and increased expression of inflammatory markers. [95]

The most commonly studied obesogens are bisphenol A, phthalates, and persistent organic

pollutants (POPs), polychlorinated biphenyls (PCBs), and dioxins.[96]

The primary mechanism through which obesogens lead to obesity seems to be the activation of peroxisome proliferator-activated receptor gamma (PPARγ) and its heterodimeric partner, the 9-cis retinoic acid receptor (RXR). [97] PPARs are members of the nuclear receptor family involved in lipid metabolism, inflammation, and metabolic homeostasis with PPARγ being involved in white adipose tissue weight increment. [98] Obesogens seem to act also through other nuclear receptors, such as glucocorticoid and steroid hormones receptors. Recent findings displayed the involvement of other nuclear receptors, induction of epigenetic modifications in fat tissue, alteration of chromatin architecture, and induction of gut microbiome dysbiosis; lots of obesogens Endocrine-disrupting chemicals are demonstrated to induce changes to the gut microbiome composition (i.e. in animals Bisphenol A have been demonstrated to reduced Clostridia in the gut while inducing an increase in Proteo- and Helico-bacteraceae). [95] These changes are linked to disorders in the immune homeostasis of the host intestine with subsequent changes in cytokine production and metabolism of liver lipids and glucose [99]The latest hypotheses have suggested that some substances could modify metabolic balance at the central, hypothalamic level by modifying hypothalamic gene regulations.[100]

Endocrine-disrupting chemicals can affect both fetal growth and subsequent action over the years, and some Endocrine-disrupting chemicals also act on the prenatal period.[101] Braun examined the relationship between early-life exposure to Endocrine-disrupting chemicals and childhood obesity.[45] A prospective birth cohort study explored prenatal exposure to PCBs by measuring their concentrations in cord blood and performing a periodical follow-up until the age of six or seven. Their study found an increased risk of being overweight in presence of higher concentrations of PCBs. [102] Phthalates were detected almost universally in human urine and in amniotic fluid, however, studies haven't demonstrated a significant association between prenatal phthalate exposure and increased fat mass in childhood. [103]

Bisphenol A is one of the most frequently researched chemicals in the pediatric population in regard to obesity development effects. literature is ambiguous about the obesogenic effects of early-life exposure[104–108] It seems to increase the expression of 11ß hydroxysteroid dehydrogenase type 1 (11ß-HSD1), which converts cortisone to the active cortisol in adipose tissues, therefore, promoting adipogenesis. Moreover, it seems to have a role in PPARγ and lipoprotein lipase (LPL) regulation. In vitro studies of omental fat in children, demonstrated increased mRNA expression and activity of 11ß-HSD1 upon Bisphenol A exposure. Likewise, an increase of PPARγ and LPL mRNA as well as lipid accumulation were found in the adipocytes. In vitro, it was also demonstrated the effect of carbenoxolone (a 11ß-HSD1 inhibitor) and RU486 (a glucocorticoid receptor antagonist) observing their inhibitory effect of Bisphenol A on 11ß-HSD1, PPAR-γ, and LPL mRNA expression. [109]Urinary Bisphenol A concentration was significantly associated with obesity in children and adolescents in different studies.[110,111]

Due to the growing evidence of Bisphenol A obesogenic effects, two similar substitutes, bisphenol S (BPS) and bisphenol F (BPF), have raised similar concerns. BPF was positively associated with a higher risk of obesity, primarily in boys with general and abdominal obesity; however, associations with BPS were not as strong.[112]

Recent meta-analysis showed that Benzophenone-3 (Bp-3) level might be a risk factor for IR in children, and obesity seems to be the mediator in the relationship between BP-3 and IR in children.[113]

5.2 Diabetogenic basis of Endocrine-disrupting chemicals related insulin resistance

Despite the role of obesogenic compounds on IR, it must be taken into account that Endocrine-disrupting chemicals can be considered diabetogenic independently of their impact on adipose tissue metabolism.[114] Diabetogenic chemicals can exert their action either by impairing insulin production or by negatively influencing peripheral insulin sensitivity. Endocrine-disrupting chemicals' actions on pancreatic function occur through several mechanisms; i.e. phthalates reduce β cell insulin content[115]; and doses of Bisphenol A of about 1 nM have been proven to stimulate glucose-induced insulin secretion in humans.[29] In animal models, Bisphenol A alters hepatic glucose sensing, impairing glucokinase (GCK) activity.[116] A meta-analysis of the cross-sectional and prospective studies from 2016 demonstrated the relationships between dioxins, PCBs and Bisphenol A levels, and diabetes; in the same study the role of phthalates was of borderline significance.[117] Insulin resistance can be provoked by various molecular patterns involved in obesogenic conditions.[118] Responses of insulin receptor substrate (IRS)-1 and IRS-2 via tyrosine phosphorylation are activated by the

presence of insulin at the cell surface. Nevertheless, insulin signaling is potentially inhibited by serine phosphorylation of these proteins by Jun N-terminal kinases (JNK) and inhibitor of nuclear factor κB (NF-κB) kinases. Various intra/extracellular sequelae of chronic nutrient excess activate these signaling pathways, linking overfeeding to insulin resistance. JNK and kinase activation triggers inflammatory cytokine production activating JNK/IKK in an autocrine-paracrine mechanism, resulting in a reinforced insulin resistance.

Endocrine-disrupting chemicals can interfere with hormones and other factors such as leptin, adiponectin, resistin, and adipsin.

Tumor necrosis factor-alfa (TNF-alfa) decreases insulin sensitivity by decreasing glucose transporter type 4 (GLUT4) function.[119] Leptin influences intracellular lipid levels in hepatic and β pancreatic cells resulting in increased insulin sensitivity (IS).[120] Resistin is a cysteine-rich protein that seems to increase in obesity, and insulin resistance, it promotes IS through TNF-alfa and IL-6 activation. [121] Among pre-β cell colony enhancing factor (PBEF) functions we can count maturation of β cells resulting in a hypoglycemic effect because of reduced glucose release from liver. PBEF levels are increased in obesity and it is known that this compound promotes adipocytes maturation mimicking insulin binding to its receptor at a different site from that of insulin. [122] Adipsin is an adipokine with a beneficial role in maintaining β function, it has been shown that higher concentrations of adipsin are associated with a lower risk of developing IR.[123] Adipsin-C3/B interaction inhibits lipolysis and glucose transportation. [124]

IR seems to be caused by inhibition of GLUT4 due to excessive expression of retinol binding protein-4(RBP-4) in abnormal adipose tissue.[125] IR determined metabolic state that induces hyperinsulinemia, which simulates transcription factors in the liver, driving hypertriglyceridemia and hepatic steatosis.[126] Hyperglycemia with reduced insulin levels was found in female subjects exposed to phthalate throughout perinatal period. [115] Studies documented the increased severity of insulitis in rats exposed to Bisphenol A during the perinatal period.[127] Endocrine-disrupting chemicals alter genome regulation during pregnancy and infancy by reducing expression of the pancreatic homeobox 1 transcription factor gene (PDX-1) resulting in an increased incidence of Diabetes[128], this phenomenon demonstrates that in utero exposure to impaired nutrition is a risk for obesity and diabetes progression in adulthood. Endocrine-disrupting chemicals also influence the distribution of essential metabolic substrates to the fetus resulting in fetal starvation, intrauterine growth retardation, and the metabolic basis of diabetes. Diethylstilbestrol exposure can lead to a deleterious fetal nutritional environment, leading to intrauterine growth retardation and influencing the later occurrence of insulin resistance. [66] [6]Prenatal and early-life exposure to Bisphenol A, perfluorinated compounds and PCBs seem to negatively affect the development of the immune system by means of both hormonal and epigenetic mechanisms, resulting in type 1 diabetes mellitus.[129,130] Endocrine-disrupting chemicals deregulate pancreatic islet beta-cell function, , influence insulin production, induce peripheral IR and compensatory hyperplasia/hypertrophy of beta cells, therefore, impairing insulin signaling and output, increasing cell apoptosis.[118] through all the above mechanisms, and possibly many more which still have to be investigated, Endocrine-disrupting chemicals induce the onset of diabetes in obese insulin-resistant individuals. [131] I.e. PCB induces pre-proinsulin expression via AHR activation and inhibition of transcription factor Nrf2a[132] while perfluorooctanoic acid significantly increases the proinsulin/insulin ratio. [117,133] Endocrine-disrupting chemicals increase the risk of insulin resistance and consequently of diabetes through modulation of glucose metabolism.[133,134]PCBs act through mitochondrial dysfunction mechanisms, including effects on pancreatic beta-cell function[135] and adiponectin release.[136] Endocrine-disrupting chemicals reduce glucagon-like peptide 1 receptor (GLP-1R) which increases the release of pancreatic glucagon via hypothalamic receptors behaving as a reducer of satiety during eating. [108] Endocrine-disrupting chemicals contribute to inflammation, apoptosis, and angiogenesis in adipose tissue as well as in skeletal muscle and liver through their influence on extracellular matrix (ECM) remodeling.[137] Excessive ECM deposition results in adipose tissue fibrosis and seems to repress expression of essential genes for adipose angiogenesis (e.g., VEGFa) by activation of ECM receptor and HIF1a/VEGFa pathways. [138] Endocrine-disrupting chemicals can also influence ER transcriptional activity by targeting the receptor directly or by regulating co-regulators. [139] Endocrine-disrupting chemicals affect quantitative insulin secretion and immunity but also alter insulin-dependent mRNA stability; since IGFBP-1 promoter regulates blood glucose levels, the upregulation of IGFBP-1 mRNA in human hepatocytes and HepG2 human hepatoma cells, even in the presence of insulin, might account for the disruptive effects of

Tetrachlorodibenzo-para-dioxin on glucose metabolism.[140]

Endocrine-disrupting chemicals reduce insulin sensitivity acting on insulin targets, especially in the liver, and on β-cell physiology; I.E. Tributyltin can reduce beta-cell mass and induce beta-cell apoptosis.[141] Oral administration of Tributyltin was shown to inhibit the proliferation and induce the apoptosis of islet cells via multiple pathways, causing a decrease of relative islet area in the animals treated for 60 days, resulting in dysregulation of glucose homeostasis.[141] Several studies have suggested adverse endocrine disruptive effects of Bisphenol A on the endocrine system as well as on pancreatic beta cells: animal studies show that pregnant mice treated with Bisphenol A during gestation, exhibit profound glucose intolerance and altered insulin sensitivity, thus becoming overweight several months after delivery, mainly through impairments in beta-cell function.[142] In vivo experiments suggest that Bisphenol A exposure increases insulin release and glucose-stimulated insulin secretion in an estrogen receptor-a (ERa) dependent mode. Several Endocrine-disrupting chemicals, including Bisphenol A and bis(2-ethylhexyl)phthalate, disrupt β-cell function, by promoting oxidative stress which significantly compromises β-cell function, as pancreatic β cells are innately more sensitive. [143] A model of immune-mediated diabetes, suggests that Bisphenol A can accelerate the exhaustion of β-cell reserve via immune modulations in pancreatic islets. As it becomes obvious, the immunomodulatory effects of Bisphenol A in mice models suggest that Endocrine-disrupting chemicals might also possibly contribute to the increasing diabetes prevalence. In 2019 a two-year toxicology study conducted as part of the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA) during any early developmental stage in rodents investigated several issues related to Endocrine-disrupting chemicals; as far as the metabolic aspect is concerned, mean body weights of females were significantly higher by 16−18% than those of the control group. [144] Since the current evidence has not conclusively established a specific cause-effect association between Endocrine-disrupting chemicals and metabolic abnormalities in the pediatric population, making more perspective studies, investigating each Endocrine-disrupting chemicals and its specific effect, but also the outcomes of exposure to mixtures of multiple Endocrine-disrupting chemicals appears to be necessary.

6. CONCLUSIONS

During the last decades, Endocrine-disrupting chemicals have become a global health problem not to be underestimated that requires attention and quick action, especially when dealing with the pediatric population. Exposure to Endocrine-disrupting chemicals starts already during pregnancy when the fetus is exposed to a large variety of Endocrine-disrupting chemicals by dietary intake or in the workplace.[145] Endocrine-disrupting chemicals exposure in vulnerable periods (that is to say during infancy) can induce adverse effects occurring in short and long terms: the years of lag time between exposure and appearance of the disease must be considered to interpret the studies and especially the understanding of Endocrine-disrupting chemicals role in neonatal outcomes as well as in the development of endocrine diseases during childhood is still an open challenge. Multiple exposures can result in cumulative effects: this outcome is expected from compounds acting via similar pathways, and probably from those acting on the same outcomes via different pathways.

The number of studies on the topic is increasing (even though it is still too low) and our knowledge of the relation between Endocrine-disrupting chemicals and Insulin resistance is becoming more and more solid throughout the passing of time, nevertheless in order to deepen our knowledge of the issue, is Important to resolve some questions.

First of all is important to investigate emerging "Endocrine-disrupting chemicals of interest" and mixtures of low-dose Endocrine-disrupting chemicals. Most of developed nations restricted the use of Endocrine-disrupting chemicals by developing regulatory measure and proposing the use of substituents to regulated compounds, but there is still lack of evidence about the safety of this substituents and new compounds (i.e., BPS and BPF as substituents to Bisphenol A, GenX as a substituent to PFOA).

Another issue to address is to establish a standardized, appropriate Endocrine-disrupting chemicals measurement method to define their presence (in terms of quantity and persistency over time) and their effects in human body; Endocrine-disrupting chemicals can be assessed in human biological fluids (serum, urine, breast milk), but their proper quantification is still a problem. Those compounds are not only agonists or antagonists of a single hormone receptor or pathway, therefore we need innovative models and tools aimed to understand how Endocrine-disrupting chemicals work: studies of Endocrine-disrupting chemicals actions on NHRs need to be extended beyond ER,

AR, PR, GR, ThR, and PPARs to other nuclear hormones, to membrane steroid hormone receptors, and to steroidogenesis, hormones and protein metabolism pathways in animal and humans models; implementation of synergistic omics techniques for biomarker discovery are also needed.

The research should also target the understanding of the epigenetic effects of Endocrine-disrupting chemicals, in terms of outcome across generations, and of dose–response functions in humans. Experimental studies, high throughput omics technologies, epidemiology and biomonitoring studies, should be integrated together to better define the connection between human health and suspected Endocrine-disrupting chemicals.

There is also the urge to create models studying absorption and distribution in the body so that we can translate results into the in vivo context and finally define whether Endocrine-disrupting chemicals cause an adverse effect in determined target tissues. The need is to perform longitudinal and multigenerational studies in both animals and humans to define the link between exposure to Endocrine-disrupting chemicals and endocrine outcomes; this is needed in order to pursue the goal of identifying and developing new strategies of prevention as well as intervention. By means of a better understanding of the molecular mechanisms underlying childhood endocrine diseases, we will supposedly be able to produce guidelines and more accurate regulatory strategies for the prevention of Endocrine-disrupting chemicals' effects (secondary) and exposure(primary) therefore ensuring health in fetuses and children not only nowadays but also in future generations. Design studies should consider gender, genetic, and population differences when assessing critical sensitive periods and different responses to Endocrine-disrupting chemicals exposures. Lastly, it might be to take into consideration the idea of creating a biobank storing different kinds of biological samples in order to start reliable long-term follow-up studies regarding metabolic/endocrine diseases or defects and other diseases.[145]

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