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PERSPECTIVE

Endocrine Disruptors and Obesity: An Overview

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Abstract: Obesity is a growing pandemic. Endocrine-disrupting chemicals are widespread in the environment. In this perspective, the authors examine the issue related to the exposure to several chemicals with endocrine-disrupting properties as promoting factors to obesity. Data show that Phthalates, Bisphenol compounds, Persistent Organic Pollutants (POPs), solvents, and personal care products can modify metabolic properties in a dose-response and sex-specific manner. Phthalates and bisphenol compounds increase body mass index, waist circumference, waist to height ratio, and the sum of skinfold thicknesses in women and not in men. Low-dose exposure to Persistent Organic Pollutants is strongly associated with increased body mass index in men and decreased this parameter in women. The mechanism through which these compounds act on anthropometric parameters is not entirely understood. Several studies suggest a possible interference in gonadotropin secretion and the thyroid axis. These inspire a decrease in both total and free testosterone levels in men and FT3 and FT4 levels in women, particularly after a pregnancy. The impact of endocrine disruptor chemicals on adipose tissue inflammation and future cardio-metabolic disorders remains to be elucidated. Therefore, studies involving both healthy and obese individuals are needed to unambiguously confirm results from in vitro and animal models.

Keywords: Endocrine-disrupting chemicals, obesity, adipose tissue, phthalates, bisphenols, persistent organic pollutants.

1. INTRODUCTION

The obesity incidence rate has more than doubled in the last decades, and nearly one-third of the world population is now classified as overweight or obese [1]. This condition represents a notable risk factor for several chronic illnesses, such as insulin resistance [2], impaired glucose metabolism and type 2 diabetes [2], dyslipidemia [2], non-alcoholic fatty liver disease and non-alcoholic steatohepatitis [2-4], hyperuricemia [5], obstructive sleep apnoea syndrome [6, 7], prothrombotic state [8], hypertension [9,10], cardiovascular diseases [11, 12], male [13] and female [14-16] fertility impairment and some types of cancer [17-19], and vitamin D deficiency [20, 21].

Obesity has a multifactorial etiology deriving from interactions among genetic, nutritional, and environmental factors [21]. The association between high calorie-dense food intake and a sedentary lifestyle leads to pathological overweight [22]. Moreover, there is evidence that exposure to several chemicals in perinatal life could represent a risk factor for obesity [23, 24] since this period of life is more susceptible to exogenous agents. Plastics, cleaning products, cigarette smoking, pesticides, and flame retardants are defined as "endocrine-disrupting chemicals" (EDCs) since they induce possible adverse effects on the endocrine system in healthy people and their offspring. Some of them are defined as "obesogens" since they affect the lipid metabolism and storage in the adipose tissue [25, 26]. For instance, tributyltin (TBT), phthalate (DEHP), bisphenol A (BPA), 4-nonylphenol, and parabens may exert estrogenic activity [27, 28] and interfere with adipogenesis by disrupting Peroxisome Proliferator-Activated Receptor (PPAR) signaling [29], whereas polybrominated diphenyl esters and other compounds could disrupt thyroid function [30].

Given the dimension of the topic and considering the widespread consumption and wastage of these chemicals in the environment, this review aims to discuss several mechanisms by which EDCs may be involved in obesity pathogenesis as possible risk factors.

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2. EDCS AND OBESITY

Grun and Blumberg demonstrated for the first time how exogenous agents can alter adipogenic pathways and energy balance, promoting an increase in adipocyte differentiation and proliferation rates [25]. To date, phthalates, bisphenol compounds, and Persistent Organic Pollutants (POPs) are considered the main compounds possibly involved in the pathophysiology of obesity.

3. PHTHALATES

Phthalates belong to a family of synthetic organic chemicals employed in manufacturing plastics, solvents, and personal care products. The prominent representatives of these compounds are Mono(2-carboxymethylhexyl) phthalate, monocyclohexyl phthalate, mono-3-hydroxybutyl phthalate, and monocarboxyisooctyl phthalate. They play a crucial role in dysregulating endocrine homeostasis and promoting body fat gain. A tight correlation between several phthalates and obesity in adults and children has been observed [31]. Studies suggest a sex-specific action of these compounds [32-34]. For instance, Vafeiadi *et al.* observed opposite effects on the body mass index (BMI), and waist circumference (WC) in boys than girls [34]. Precocious exposure to phthalates is associated with lowering BMI, WC, and waist-to-hip ratio in boys but not in girls [34]. Additionally, a longitudinal study on 1239 girls aged 6-8 years showed similar results [35]. However, the results of a recently published meta-analysis of observational studies showed a slight correlation between phthalate exposure and body mass outcomes, especially in children [36].

4. BISPHENOL COMPOUNDS

Bisphenol compounds, such as BPA, BPF, and BPS, are some of the most widespread synthetic chemicals employed in plastics manufacturing [37, 38]. Several studies demonstrated that BPA exposure could significantly affect anthropometric parameters, increasing WC and BMI, thus promoting abdominal obesity [39, 40]. Early-life exposure to bisphenols may be associated with fat mass gain, hypertriglyceridemia, and high circulating levels of free fatty acids, especially in rodents. This effect was robust after exposure to bisphenol over the current reference dose of 50 μg/kg/daily [41].

Continuous exposure to these compounds could modify metabolic properties, fostering abdominal obesity and overweight in humans. Using data from the US National Health and Nutrition Examination Survey (NHANES) from 2013 to 2016, Jacobson *et al.* evaluated the association between urinary bisphenols compounds (a biomarker of cumulative exposure to bisphenols) and anthropometric parameters in children and adolescents aged 6 to 19 years. Urinary concentrations of BPS and BPF, but not BPA, were associated with a higher WC and increased BMI z-score overall [42].

Due to its similarities with estrogen structure, BPA can exert sex-specific effects on body mass [43]. For example, a prospective study evaluated a positive association between urinary BPA and the sum of skinfold thickness in women but not in men [33]. Furthermore, an increased risk of central adiposity in 7-year-old girls was related to maternal BPA exposure during pregnancy [44].

A comparative study performed in adults by using the NHANES data from 2013 to 2014 shows a significant positive relationship between BPA exposure [44], but not BPF and BPS, and excessive fat accumulation [45, 46], thus increasing BMI and WC and raising the risk of abdominal obesity [47, 48].

5. PERSISTENT ORGANIC POLLUTANTS (POPS)

Persistent organic pollutants (POPs) include polychlorinated biphenyls, organochlorine pesticides hexachlorobenzene, and p,p-dichlorodiphenyldichloroethylene (DDE) (primary metabolite of DDT). The CHAMACOS study represents a relevant study evaluating the interaction between POPs and the adipose tissue. This longitudinal birth cohort study was performed on 527 pregnant women and their offspring and found a significant correlation between EDCs' exposure, including DDT, through fetal life and increased BMI and WC in 9-year-old girls. This could represent a significant risk factor for metabolic syndrome in adulthood [49]. The prenatal window is one of the most vulnerable periods of life, especially for adipocyte development. Exposure to a low dose of POPs during this period of life could raise the risk of fat accumulation in children. Mainly, in utero exposure to DDE and HBC, but not to PBC's, drives an increase in BMI and WC in 4-year-aged children [50]. Furthermore, a non-monotonic dose-exposure response has also been described. For instance, adverse effects of these compounds were induced in the case of low-dose exposure to POPs. Conversely, high-dose exposure seems to be inversely associated with abdominal obesity [51, 52]. POPs, as well as other EDCs, act in a sex-specific manner. They pointed out the action of oxychlordane and DDT on BMI and WC in both samples. Notably, according to Elobeid *et al.*, oxychlordane is associated with a BMI increase in men and a BMI decrease in women [52]. On the contrary, DDT was associated with a WC decrease in males and a WC increase in females [53]. This might be due to hormonally directed differences in fat storage among men and women: although women are prone to accumulate fat in their hips, men are predisposed to store it at the waist level.

6. DISCUSSION

6.1. The Pathogenesis of Obesity: Interaction between Edcs and Adipogenesis

Adipose tissue was previously considered a storage tissue only, but it is now clear that it is fully involved in metabolic and endocrine homeostasis [52, 54]. The differentiation of mesenchymal stem cells into adipocytes is crucial since it defines the pathophysiology of obesity. The development of mature adipocytes occurs in a series of ontogenetic steps. Initially, mesodermal cells are differentiated from pluripotent embryonic stem cells that change into multipotent fibroblasts. Then, they could be converted into unipotent preadipocytes. Finally, these are differentiated into mature adipocytes due to the activation of PPAR [55]. BPA, phthalates, and TBT are widespread EDCs. Notably,

due to their lipophilic nature, they are mainly stored in the adipose tissue. A significant body of evidence demonstrated that exposure to phthalates, 4-nonylphenol, and BPA could alter normal lipid metabolism and adipogenesis [56], operating on adipocyte differentiation or proliferation in murine cell lines [57, 58]. Indeed, these molecules affect adipogenic differentiation of mesenchymal stem cells (C3H/10T1/2) in a concentration-, stage- and compound-specific manner [29]. More specifically, TBT could reversibly bind to PPAR-γ and Retinoid X Receptor (RXR) [29], and it may mediate the related signaling pathway in *in vitro* [59] and mouse models [60]. PPAR-γ is a nuclear receptor that enhances gene expression promoting fatty acid storage in adipocytes. Additionally, it inhibits gene expression related to stimulation of lipolysis and promotes insulin-sensitivity [61]. RXR ligands act similarly [62], highlighting the potential effects on obesity of both PPAR-γ and RXR agonists. TBT acts as a dual ligand for permissive heterodimers such as RXRα/PPAR-γ. Given this mechanism, possible additive or synergistic effects increasing the potency of these compounds have been described *in vivo* [63]. Even though the mechanism by which EDCs induce an increase in adipocytes number *in vitro* is well-known [29, 56, 58], it is still unknown which factors induce the same phenomenon *in vivo*. It might result from an increase in adipocyte precursor cell number or maybe the consequence of an increase in adipocyte size without an increase in the number or a combination of both [63]. Further studies on humans are needed to explain these phenomena better.

6.2. Anti-androgenic and Estrogenic Effects of EDCs and Obesity

EDCs' gender-specific action on human metabolism might depend on their molecular structure. Many compounds such as BPA, phthalates, and flame retardants display molecular similarities with synthetic estrogens. Due to this chemical similarity, most of them can interact with estrogenic receptors modulating sex steroid hormone actions in men and women. Gravel *et al*. demonstrated that a relevant professional exposure to these compounds increases the risk of sex hormone dysregulation contributing to the pathophysiology of obesity. Their study shows that a higher urinary concentration of OPE-related metabolites is associated with a decrease in both total and free testosterone levels and an increase in estradiol (E2) in men [30]. By contrast, no relevant associations were found in women [30]. Furthermore, a cross-sectional study of Chinese workers confirmed these data in men. Notably, it shows that exposure to DEHP, DBP, MEHP, and MBP induces a decrease in serum free testosterone, not followed by a compensatory increase in LH and FSH [64], suggesting a possible alteration in the hypothalamic-pituitary-testicular axis. Short-term professional exposure to phthalates also seems to reduce total serum testosterone levels in men [65]. Nevertheless, according to NHANES data from 2013 to 2016, these effects vary according to men's age [66]. Exposure to high-molecular-weight phthalates was associated with lower total, free and bioavailable testosterone among men ≥ 60 years. By contrast, low-molecular-weight phthalate exposure was associated with lower total, free and bioavailable testosterone among younger men (*i.e*., 20-39 years).

The leading mechanism of sex hormone disturbance is still unclear. Several studies suggest that EDCs play as steroid antagonists on estrogen and androgen receptors [67]. Moreover, EDCs were found to upregulate the aromatase enzyme activity, thus enhancing testosterone conversion to estrogen [68]. In this way, lower serum testosterone concentration reduces the risk of fat accumulation in women and predicts a more significant weight gain in men.

6.3. The Relationship between Obesogens, EDCs, and Thyroid Hormones

EDCs may affect each endocrine organ, including the thyroid gland. For instance, hypothyroidism predisposes to weight gain, and the contrary is observed in hyperthyroidism [69]. In the Puerto Rico Test site for Exploring Contamination Threats (PROTECT) birth cohort, Johns *et al.* reported an inverse association between meta-chlorophenylpiperazine and free triiodothyronine (T3) levels and a positive association between mono-benzyl phthalate and thyroid-stimulating hormone (TSH) during pregnancy [70]. This phenomenon can partly explain why lower weight loss was observed in post-pregnancy women exposed to these substances regardless of baseline BMI after a year from birth. Accordingly, a recent study by Perng W *et al.* investigated the effect of EDCs' exposure in 199 pregnant women from Mexico City and showed lower weight loss after one year from birth compared to controls [71]. The same result was confirmed by a cohort study (ELEMENT project), particularly after exposure to meta-chlorophenylpiperazine [72]. Difficulty in losing pregnancy-related weight gain could potentially be related to EDC-mediated thyroid hormone imbalance or the activation of PPAR-γ nuclear receptors.

TBT, a pesticide commonly used in agriculture, is another EDC affecting thyroid hormones. TBT modifies thyroid function either directly or indirectly by influencing the hypothalamus-pituitary-thyroid axis. In this way, it alters TSH secretion interfering with endogenous hypothalamic TRH in rats [73]. Furthermore, the isoforms of RXR and PPAR-γ have been described as regulators of the hypothalamic TRH gene, and this suggests a possible alternative mechanism for the action of TBT on the HPT axis [74, 75]. As a result, it can induce weight gain by reducing T3 and T4 levels and acting as a PPAR agonist.

6.4. EDC Exposure During the Perinatal Window

The perinatal period is a critical window for adipocytes development. This is relevant since the epigenome is still malleable and can receive and store signatures originating from the maternal environment. Exposure to toxic compounds during this time induces significant effects on health status. For instance, exposure to cigarette smoke *in utero* is a risk factor for obesity later in life. A large prospective cohort study underlines maternal smoking during pregnancy and postnatal life involves the risk of overweight in children at age seven years in a clear dose-response manner [76].

EDC exposure could further affect newborn body weight. Indeed, it has been detected that a higher urinary concentration of BPA during the gestational period is relat-

ed to an increase in central adiposity in childhood, particularly in girls [77]. Furthermore, low birth weight is considered a risk factor for obesity in adulthood. A large meta-analysis investigated the association between EDC exposure during pregnancy and offspring birth weight. Birks *et al.* suggested that the toxic effect of exogenous compounds during the perinatal window induces low birth weight in newborns [78, 79], which could represent a risk factor for overweight later in life. Another mechanism through which EDCs interfere with metabolic homeostasis is the alteration of adipokine assets. Adiponectin is a white adipose tissue-released hormone which plays an anti-inflammatory, insulin-sensitizing role [80]. Lower adiponectin levels induce pathological fat accumulation and insulin resistance, driving the metabolic syndrome [81]. Next to adiponectin, leptin is also produced by white the adipose tissue. This hormone, secreted parallel to fat accumulation, plays a key role in hypothalamus pathways promoting the sense of satiety [82]. A longitudinal cohort study on 1363 subjects highlighted the adverse effects of phthalate exposure on adipokine patterns, such as leptin and adiponectin. Positive and negative relationships between mono-(3-carboxypropyl) and leptin and adiponectin were found in males, respectively. By contrast, leptin levels in women show more vulnerability to monobenzyl phthalate action [83]. Additionally, the regulation of gene expression for adiponectin secretion in children is also influenced by BPA [84]. In this way, these pathways could promote pathological overweight and insulin resistance in adults [85] and children [82].

6.5. EDC Exposure and Adipose Tissue Macrophages

Adipose tissue is a key factor in the pathogenesis of cardio-metabolic diseases [86]. Adipose tissue distribution affects cardiometabolic risk, as visceral distribution remarkably increases this risk [87, 88]. Adipose tissue morphology is another well-established determinant of atherosclerosis and cardio-metabolic risk [89]. Relevant histological and functional dissimilarities characterize the white and brown adipose tissues. The former is composed of unilocular white adipocytes with scarce mitochondria, acts as an energy store, and represents the main component of visceral and subcutaneous adipose tissue [90]. Brown adipose tissue is mainly expressed at cervical, supraclavicular, axillary, paravertebral, and suprarenal levels. It is characterized by multilocular and mitochondrial-rich brown adipocytes and plays an essential role in energy expenditure and heat output [90]. Browning of adipose tissue is a well-recognized phenomenon of gene expression reprogramming consisting of white to brown-like (beige or brite) transition under environmental (*i.e.*, cold) and pharmacological (*e.g.*, beta3-adrenergic activation, PPAR agonists) conditions, and after exposure to physical exercise and certain foods [91-93]. Overnutrition induces adipose tissue enlargement and triggers inflammation as a sort of adaptive mechanism [94]. The pathophysiology of this phenomenon remains unclear (*e.g.*, local hypoxia, genetic background) but is implicated in the pathogenesis of insulin resistance, type 2 diabetes, arterial hypertension, and cardiovascular complications [95, 96]. Macrophages are the leading component of immune cells in the adipose tissue of obese individuals. They play a fundamental role in obesity-related local and systemic inflammation, particularly M1-polarized macrophages [97]. These macrophages secrete TNFα and IL-1beta, that, in turn, contribute to local and systemic insulin and catecholamine resistance [95]. As an alternative, IL-4 induces polarization of adipose tissue macrophages in the M2 sense. M2-polarized macrophages secrete catecholamines and are, therefore, involved in adipose tissue browning. Hence, the M1-to-M2 ratio could be a key regulator of adipose tissue homeostasis, energy balance, and local and systemic inflammation [97, 98].

To our knowledge, the macrophage poll in the adipose tissue is replenished by self-renewal of local stem cells with only a scarce peripheral contribution (*i.e.*, peripheral monocytes). Therefore, the total number of macrophages in the adipose tissue largely depends on the intrinsic balance between self-renewal and degradation by innate lymphoid cells [99]. Self-renewal exceeds the macrophages degradation rate in obese individuals. As a result, mature adipose tissue macrophages are more represented in obese than lean individuals [99]. This phenomenon could be considered a (mal) adaptive response to overnutrition and adipose tissue expansion and may strengthen local and systemic inflammation.

Preclinical studies have demonstrated that EDCs may disrupt the regulation of macrophage self-renewal. BPA increased macrophage self-renewal in mice models by binding to the liver receptor Xα, highly expressed on quiescent macrophage surface in the adipose tissue [100]. In addition, in an *in vitro* study, macrophages cultured with BPA exhibited a marked and dose-dependent inflammatory response (IL-1β, IL-6, and TNFα) than controls via ERK-NFκB and JAK1/2-STAT3 pathways [101]. BPA promotes macrophage proinflammatory patterns by enhancing M1 polarisation whilst suppressing M2 polarisation *via* the interferon regulatory factor 5 (IRF5). Similar findings were obtained from another *in vitro* study using different EDCs, including diethylstilbestrol, BPA, bis(2-ethylhexyl) phthalate, and p-nonylphenol. A dose-response correlation was also confirmed with a maximum response at 10^{-7} M [102]. Opposite results were induced by the phthalate diethylhexyl-phthalate as, in *in vitro* and animal models, it promoted M2-polarization of macrophages [103-105].

Thus, EDCs exposure could influence the levels of adipose tissue inflammation predisposing to atherosclerosis and cardio-metabolic diseases [106, 107]. So far, evidence has been obtained from pre-clinical observations with opposite results by different EDCs (mostly phthalates vs. BPA). In addition, the effect of simultaneous exposure to a mixture of different EDCs has not been investigated, and studies involving humans are not currently available. Although it is a current topic, not enough evidence has been provided to draw a clear conclusion.

CONCLUSION

In conclusion, exposure to obesogenic compounds such as bisphenols, phthalates, POPs, and TBT may modify metabolic properties and possibly predispose to obesity by disrupting hormonal metabolism and signaling [108]. The earlier the exposure to EDCs, the greater the risk of metabolic consequences. Gender dimorphism is possibly involved in

the metabolic consequences of EDC exposure. The role of EDCs in inducing or modulating adipose tissue and systemic inflammation should be better elucidated, possibly by long-term observational human studies.

LIST OF ABBREVIATIONS

BPA	=	Bisphenol A
BMI	=	Body Mass Index
DDT	=	Dichlorodiphenyldichloroethylene
EDCs	=	Endocrine-Disrupting Chemicals
NHANES	=	National Health and Nutrition Examination Survey
PPAR	=	Peroxisome Proliferator-Activated Receptor
POPs	=	Persistent Organic Pollutants
DEHP	=	Phthalate
RXR	=	Retinoid X Receptor
TSH	=	Thyroid-Stimulating Hormone
TBT	=	Tributyltin
WC	=	Waist Circumference

AUTHORS' CONTRIBUTION

I.M. and G.D.P. conceived the review; I.M and G.L. drafted the manuscript; I.M., G.L., G.D.P., R.Z., V.T. searched databases and selected appropriate results; G.L. and I.M. handled the manuscript revision in response to the reviewer's comments; all the authors read the text, provided feedback and accepted the final version of the manuscript.

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