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Review Article

THE STOLEN DREAMS, ENDOCRINE DISRUPTING CHEMICALS AND CHILDHOOD OBESITY

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Abstract:
For the sake of our future and our children, we need to strive for an answer about the role of complex synthetic chemicals that are involved in our daily life on our health. Such chemicals were supposed to provide replacement for classical materials used in the synthesis of many things that surrounds us, including the food utensils. This effect is extended to include the childhood obesity. The answer is composite; it does not only require the efforts of the epidemiologists but also the physiologists, molecular biologists and geneticists. There is mounting interest in understanding the impact of the environmental contaminants and endocrine disrupting chemicals (EDC) in obesity, because by definition these are preventable once identified. Human studies to environmental exposure to EDC in relation to obesity among children need to be encouraged. We need to understand the subtle damage they may cause and the obscure role they play in the children obesity epidemic.

Keywords: Children obesity, plastics, bisphenol A, phthalate

Introduction: The global Crisis

Overweight and obesity are defined by the WHO (World Health Organization) as abnormal or excessive fat accumulation that presents a risk to health[1]. Obesity has dramatically increased worldwide in the recent decades, and becoming a major global health concern. Like adults, the prevalence rate for child and adolescent obesity has increased all over the world [1]. Childhood obesity is on the rise and considered as serious health problem worldwide[2-4]. Furthermore, it is considered a risk factor for many health problems that appear later in life such as heart disease, hyperlipidemia, hyperinsulinaemia, hypertension, and early atherosclerosis[5-7].

The international standards for overweight and obesity developed by the International Obesity Task Force in 1997, are based on the body mass index which is defined as follows : BMI = (weight/height^2) and is

widely used in adult populations, and a cutoff point of 30 kg/m^2 is recognized internationally as a limit of adult obesity. Body mass index in childhood changes substantially with age[8,9]. At birth the median is as low as13 kg/m^2, increases to 17 kg/m^2 at age of 1 year, decreases to15.5 kg/m^2 at age 6 years, then increases to 21 kg/m^2 at age 20 years old[10]. An international standard with BMI cut-off points for each age and sex was proposed in 2000 based on a pooled representative sample of children from six countries, including different ethnic origins[10]. This standard has the advantage of being continuous with the adult range, since at the age 18 the cutoff point of 25 kg/m^2 for overweight and 30 Kg/m^2 for obesity merge those used in adults.

Increased rates of overweight and obesity among children have been observed globally; the Middle East has its share in this global epidemic. In a national surveillance in the United Arab Emirates (UAE), the prevalence of overweight was estimated to be 21.5% and the prevalence of obesity was estimated to be 13.7% among children aged 5-17 years[11]. In Lebanese children aged between 6 and 8 years, the prevalence of overweight and obesity is 25.5% and 6.5%,respectively[12].In Saudi Arabia, the latest national data revealed that the rates of overweight and obesity among school-age children have reached 23% and 9.3%, respectively. However, the rates of overweight and obesity among preschool children were reported as approximately 15% and 6%, respectively[13].

Obesity is the result of a prolonged disturbance in the homeostatic regulation of energy metabolism that favors *triglyceride storage* and *adipocyte hypertrophy*. The number of adipocytes is also greater in obese individuals, implicating increased adipogenesis or hyperplasia as contributing to fat mass. Measurement and modeling of fat cell dynamics via radionuclide tracing suggest that increased adipocyte number is largely established by early adulthood. This is a consequence of an earlier onset and increased adipocyte expansion [14;15].

Since obesity is associated with sedentary lifestyle patterns and inadequate dieting behaviors, obesity has been thought to be explained by a prolonged positive energy balance. However, this idea is now being challenged, as several social, economic and environmental factors have been shown to influence human physical growth and development. Intriguingly, obesity is one of many diseases that were shown to have a developmental origin[16]. In particular, obesity may be increasing as a function of developmental nutrition and exposure to environmental chemicals during the critical early life period. These compounds interfere with the body's adipose tissue biology and interact with hormone receptors. They mimic or antagonize the actions of endogenous hormones, thus disrupting the programming of endocrine signaling pathways during critical windows of early development and differentiation. As a consequence, they are commonly defined as endocrine disrupting chemicals (EDC).Infants and children may be considered a highly susceptible population to EDC exposures[16-23].

From the beginning of the last decade, it has been suggested that toxic chemical agents may contribute to the increased frequency of obesity in the population. Analyzing the correlation between increased frequency of obesity in the population and increased production of industrial chemical substances, led to the hypothesis of a causal relationship between both obesity and the environments chemicals. The term *obesogens* was subsequently coined to designate chemical substances that pollute the environment and when those chemicals access the body, a disturbance in energy regulation might result[24].

Obesogens are xenobiotics that may occur in the environment and/or food and that inappropriately regulate and promote lipid accumulation and adipogenesis[25]. Several recent studies have addressed the potential impact of the endocrine disruptor effect of the energy regulation system, *i.e.* obesogens and their relation to the increase in obesity prevalence in virtually all countries of the world[26]. Obesogens may cause obesity in several ways including disruption of critical lipid metabolism pathways to promote adipogenesis and fat storage, the alteration of the metabolic set point to induce positive energy balance, or increasing appetite[27]. *Phthalates and Bisphenol A* are examples of commonly encountered chemicals which may have negative impact on lipid and adipose homeostasis in adults as well as in children.

Phthalates

Phthalates are a widely used class of chemicals that are dialkyl- or alkylarylesters of 1, 2 benzenedicarboxylic acid[28]. They are divided into two distinct groups, with different applications, toxicological properties and classifications. High molecular weight phthalates (High- MWP) such as di (2-ethylhexyl) phthalate (DEHP) or di-iso-nonylphthalate (DiNP) are added to plastics to enhance their flexibility and durability and often referred to as plasticizers. Typical products containing these phthalates include floorings, roofing, wall coverings and cables, clothing, packaging materials, toys, furniture and car upholstery. Low molecular weight phthalates (Low-MWP) including diethyl phthalate (DEHP) and di-n-butyl phthalate (DnBP) are used in adhesives, detergents, and solvents and are present in some medicines (tablet coating, capsules), personal-care products, cosmetics, fragrances and nail polish[28;29]. Interestingly, although phthalates are known to disrupt the endocrine signals, studies failed to show that phthalates bio-accumulate inside the body[30]. Humans are exposed to these compounds via multiple routes; i.e. through food and water (oral), through air (inhalation) and through body care products (dermal) [28].

Further to the studies of phthalates-mediated obesity in humans, in utero study revealed that mice-off spring experienced increase in visceral fat after their exposure to DEHP at a dose of 0.05 mg/kg body weight per day, which is an environmentally relevant dose[31]. Also body weight of female offspring at this dose was elevated. At a higher dose (5.0 mg/kg body weight per day), visceral fat weight was still increased in females, but decreased in males. Body weight in females, at this dose, was higher compared to controls, and also in males a significant increase in body weight compared to controls wasobserved[32].

Phthalates are the most likely to act through peroxisome proliferator- activated receptors to cause adipocyte conversion. These receptors are a group of three isoforms which are located inside the nucleus and encoded by different genes. The three isoforms play a critical physiological role as lipid sensors and regulators of lipid metabolism, while the gamma isoform (PPARγ) can react with phthalates and activates the downstream signaling pathway[33;34].

As the case of nearly all nuclear hormone receptors, PPARγ can be perturbed by environmental chemicals. PPARγ is perhaps even more susceptible than most nuclear receptors because its ligand binding pocket is large and can accommodate a diversity of chemical structures[35]. Since PPARγ is a master regulator of adipogenesis, a logical hypothesis is that inappropriate activation of the receptor contributes to obesity [36].

Emerging evidence suggests that childhood exposure to phthalates may increase the risk of obesity. In a study by Hatch and his colleagues [37], Body Mass Index (BMI) and

waist circumference (WC) increased with urinary phthalate metabolite concentration among female girls in the United States. Two recent studies using data from National Health and Nutrition Examination Survey (NHANES) found that urinary levels of LMW phthalates were associated with higher odds for obesity in children and adolescents[38;39]. In addition, a prospective cohort study found that the urinary concentration of LMW phthalate metabolites was positively associated with BMI in overweight children[40].

Bisphenol A

Bisphenol A (BPA), which is widely used chemical in food containers, has been linked to childhood obesity. BPA was used since the 1960s in the manufacturer of babies' bottles, beverage bottles and food containers as well as a coat for metal cans. BPA mimics estrogen action through binding to its nuclear receptor. At the same time, BPA interferes with many hormones including androgens and thyroid hormones[41;42]. Upon BPA oral administration, possibly as a contaminant of food, a complete absorption occurs from the gastrointestinal tract, followed by its transport to the liver for conjugation, which results in soluble metabolites ready for excretion via kidneys[43]. As a consequence and due to the immaturity of the enzyme responsible for conjugation 'glucouronidase', newborn have 3 times the concentration of BPA in comparison to adults. The BPA increased levels were only observed in bottle-fed babies with polycarbonate bottles [44]. In accordance, these observations led to the frequent appeals of banning BPA products from the infants and children products.

In literature, there is a worldwide studies measured the level of BPA in the school age children encouraged by the non-invasive sampling of 'morning urine', and the feasibility of the measurement technique of BPA metabolites. Harley et al reported increased the level of urinary BPA among young girls was associated with increased adiposity[45]. BPA has been shown to induce the enzyme 11β-hydroxysteroid dehydrogenase type 1 in children. This enzyme converts cortisone to cortisol, the active form that promotes adipogenesis[46]. In addition, BPA has shown to decrease DNA methylation in the promoters of certain genes, which was associated with change of the experimental mice coat color obesity and diabetes [47].

In Germany, a study on children from 3 to 14 years old detected BPA in the urine of 599 from 600 studied samples [48]. Trasande et al conducted a study on 2838 children between the ages of 6 and 19 years old. The authors showed increased levels of urinary BPA concentration was associated with higher body mass index. The association was highly significant with the white ethnicity in comparison to black or Hispanic[49]. Similar finding was also obtained from another study in USA by Bhandari and coworkers with special predominance in boys [50]. The same trend was demonstrated in China by Wang et al and Li et al in school children [51;52].

Furthermore, BPA based fillings were preferred by dentists for children. BPA is hydrolyzed and detected in saliva, which can be another source that increases the level of this endocrine disruptor in the body. As a preventive measure, Fleisch et al recommended to minimize the use of these fillings as well as requested the manufacturer companies to provide detailed description of their constitutes [53].

In addition, the repeated exposure to BPA for many years and on daily basis could be associated with other complications; for example, renal affection has been found in Chinese children exposed to BPA. These children had higher micro albumiuria in comparison to the controls, which indicates renal endothelial dysfunction [49]. The effects

are not only confined to obesity or renal affection but also extend to even cancer development [54].

Conclusion

Children obesity is a colossal concern as it predisposes to various health problems, which are linked later with adult morbidity and mortality. Previously, the child obesity prevention programs were mainly focusing on promoting the physical exercise and cutting down calories, while it has been proposed recently that endocrine disrupters such as Phthalate and BPA have a significant role in the drastic increment of child obesity incidence.

Various studies have proved the relation between the levels of urinary phthalates and BPAs to children obesity; however, more validation is required by relating the active forms levels in the serum with the child obesity. An additional and crucial factor need to be considered, which is the time of collecting the urine samples from the population, because it was found that phthalates and BPA metabolites urinary excretion varies in different times of the day [55].

Extended research is substantially needed to determine which metabolites, at which concentration and at which time, increase the risk. Based on that, health authorities can implement certain health policies to prevent these silent invaders from steeling our future, children.

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