Urinary Phthalate Levels in Relation to Obesity among a Sample of Egyptian Children

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Abstract

**BACKGROUND:** Childhood obesity is considered a risk factor for chronic diseases later in life. Phthalates (phthalate acid esters), predominant constituents of plasticizers, are well-thought-out global environmental contaminants. Phthalates can cause adverse health effects, including obesity, hypertension, and cardiovascular diseases. The present study aimed to investigate the relationship between obesity and phthalates in children in Egypt.

**AIM:** The study's objective was to examine the association between obesity and urinary phthalates levels in a sample of Egyptian children.

**MATERIALS AND METHODS:** This cross-sectional study included 210 children; 71 children were obese. Age ranged between 8.8 and 16 years with a mean of 12.93 ± 1.29 years. Sociodemographic data were collected. The examination included measuring body weight, height, waist and hip circumferences (WC and HC), and calculation of BMI. The lipid profile was analyzed. Urine samples were tested for phthalate metabolite levels using high-performance liquid chromatography.

**RESULTS:** Urinary phthalate metabolites mono benzyl (MBzP), monobutyl (MBP), monoethyl (MEP), and mono-(2-ethylhexyl) phthalate (MEHP) were detected in all urinary samples with varying levels. The median concentrations of MBzP, MEHP, MBP, and MEP were 1.4, 54.5, 29.9, and 490 (ng/ml), respectively. In obese children, urinary MBzP, MEP, while urinary MBP demonstrated a significant positive association with serum triglycerides levels. Obesity as body weight, BMI, WC, and HC were significantly positively correlated with urinary levels of MEHP and MEP, while urinary MBzP demonstrated a significant positive association with serum triglycerides levels.

**CONCLUSION:** The present study suggests an association between phthalates exposure and childhood and adolescent adiposity.

Introduction

Childhood and puberty are critical periods for adipose tissue mass building [1]. The worldwide prevalence of overweight and obesity in children has amplified over the past three decades to 124 million [2] and WHO predicts by 2025 an additional 70 million [3]. Obesity in children and adolescents does not only disturb their health and social life but may have resounding adverse effects during forthcoming adulthood [4]. People with obesity may suffer one or more chronic diseases such as Type 2 diabetes mellitus, hyperlipidemia, cardiovascular disease, liver and gall bladder diseases, stroke, hypertension, and specified types of malignancies [5].

Besides the modern rise in popularity of fast-food and physical inactivity, exposure to environmental pollutants has been linked to childhood obesity [6]. Exposure to endocrine-disrupting chemicals as phthalate acid esters throughout this period may have harmful consequences on adipose function and metabolism [7], [8], [9]. Phthalates are commonly used as plasticizers in household products. They are utilized in the production of widely-distributed personal tools such as children’s toys, paints, cosmetics, and food packages [10]. Phthalates easily leach from their compounds and enter the human body through ingestion, inhalation, and dermal contact [11], [12]. Children have been suggested to be more susceptible to exposure, mostly due to diverse behavioral attitudes and higher consumption in relation to body size [13]. Phthalates association with several human diseases are currently an eminent subject in the literature [14]. The evidence on the association of phthalates with obesity and lipid metabolism is limited and inconsistent [15].
The present study aimed to investigate the relationship between obesity in Egyptian children and phthalates exposure. This study also assessed the associations of urinary phthalate with physical (body mass index [BMI], waist and hip circumferences [WC and HC]), and biochemical indices of obesity (total serum cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides [TG]).

Materials and Methods

This study was conducted at the National Research Centre (NRC) in Egypt, as a part of a research project funded by NRC [16]. It was a cross-sectional study, comprising 210 children of both sexes. Age ranged between 8 and 16 years. They were randomly selected from Giza governorate schools from October 2017 to April 2018. All were more or less of similar social class. Exclusion criteria included liver diseases, renal diseases, thyroid disorders, and endocrinal or genetic causes of obesity.

Ethical issues

Permission to implement the study was approved by the Ministry of Education and the director of the school of children included in the research. Ethical approval of The Research and Ethical Committee of the NRC was obtained (Number: 16368). Parents were informed about the purpose of the study and their written consents were obtained.

Sociodemographic history and clinical examination

The participants were asked to complete a structured questionnaire. Questions included sociodemographic variables and medical history. Children were subjected to thorough clinical examination that included chest, heart, abdominal, and neurological examination. Anthropometric measures after the recommendations of the International Biological Program were assessed.

Anthropometric measurements

Bodyweight (kg), height (cm), WC, and HC (cm) were measured. The height was measured to the nearest 0.5 cm using a Holtain portable anthropometer. The weight was measured to the nearest 0.1 kg using scale balance while the child was dressed in minimal clothes and without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. WC was measured at the level of the umbilicus while the participant standing and breathing normally. HC was measured at the level of the iliac crest using non-stretchable plastic tape to the nearest 0.1 cm. Each measurement was taken as a mean of three consecutive measurements using standardized equipment and following the recommendation of the International Biological Program. Children were considered obese when their BMI Z score was higher than +2 for age and gender according to the WHO Child Growth Standards [17].

Laboratory investigations

Determination of phthalates using high-performance liquid chromatography.

Phthalates are metabolized to their monoesters within a short period, urinary phthalate monoesters are considered valid biomarkers for evaluating human phthalates exposure [18], [19]. One spot urine sample is sufficient to represent exposure over 6 months to permit its usage as an exposure estimate in epidemiological research [8], [20], [21]. To adjust for dilution, we included urinary creatinine as a covariate in all analyzes. All metabolite concentrations were adjusted for creatinine levels and expressed as μg/g Cr.

Phthalates metabolites were measured instead of their parent compounds to lower the potential for exposure misclassification. A grouping of solid-phase extraction, high-pressure liquid chromatography, and tandem mass spectrometry was used to estimate phthalates metabolite concentrations using methods defined by Koch et al. [18]. Urine samples were thawed and sonicated for 10–15 min, then (100 μl) was loaded into a glass vial (2 ml) contained ammonium acetate (AA, 20 μl, >98%, Sigma Aldrich Laboratory, Inc., St. Louis, MO, USA), β-glucuronidase (10 μl, E.coli K12, Roche Biomedical, Mannheim, Germany), and a combination of ten isotopic 13C4 phthalate metabolite standards (100 μl. Cambridge Isotope Laboratory, Inc., Andover, MA, USA). Afterward, the samples were incubated (37°C, 90 min), a 270 μl solution (5% ACN), Merck, Darmstadt, Germany) with 0.1% formic acid (FA, Merck, Darmstadt, Germany) was added and sealed with the PTEF cap for analysis.

Monoethyl phthalate, monomethyl phthalate, monobenzyl phthalate, monobutyl phthalate, and bis-2ethylhexylphthalate were purchased from Sigma-Aldrich. β-glucuronidase was purchased from Roche. Stock solutions of standards were prepared in acetonitrile (3000ng/ml). Eleven-point calibration curve was constructed for each standard (0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and 1000 ng/ml).

Sample preparation was done by solid-phase extraction according to the method described by Feng et al. [22]. After evaporation of eluting, the residue was reconstituted in 100 μl 20% acetonitrile in water and injected.

Analysis was done on Waters Xevo TQD – ESI.
Results

This study included 210 school children, 118 boys, and 92 girls. Their age ranged between 8.8 and 16 years with a mean of 12.93 ± 1.29 years. Their anthropometric and the clinical data included the body weight (kg), height (cm), WC and HC (cm) and serum triglycerides (mg/dl), cholesterol (mg/dl), HDL (mg/dl), and LDL (mg/dl) are shown in Table 1.

Table 1: Age, anthropometric, and biochemical data of the studied children

|          | Minimum | Maximum | Mean | Std. Deviation |
|----------|---------|---------|------|----------------|
| Age      | 8.80    | 16.00   | 12.907 | 1.28654        |
| Weight (kg) | 20.00  | 109.00  | 54.508  | 16.31442       |
| Height (cm) | 100.00 | 184.00  | 152.842  | 12.31531       |
| HAZ      | -3.19   | 3.55    | -0.3483 | 1.35522        |
| BAZ      | -3.66   | 4.58    | 1.0820  | 1.67432        |
| Waist circumference (cm) | 47.00 | 111.00  | 75.8241  | 13.08472       |
| Hip circumference (cm) | 54.00 | 131.00  | 89.8054  | 14.03400       |
| Triglycerides (mg/dl) | 67.80 | 311.90  | 97.2231  | 63.07140       |
| Cholesterol (mg/dl) | 114.40 | 243.70  | 187.4731 | 40.00857       |
| HDL (mg/dl)    | 35.00  | 65.00   | 49.88   | 8.18451        |
| LDL (mg/dl)    | 55.00  | 177.00  | 116.05  | 35.627         |

The urine of children with obesity had higher significant concentrations of MBP, MEP, and MEHP than the urine of normal-weight children (Table 5).

Discussion

Association between phthalates exposures and obesity in adults and children has been pointed out in the previous literature with conflicting results [26, 27]. The extensive phthalates exposure of humans was demonstrated through quantifying phthalates metabolites in urine samples, where the levels of urinary phthalates metabolites indicate recent exposure [28]. In this study, low molecular weight metabolites MBzP, MBP, MEP, and high molecular weight metabolites (MEHP)
were detected in urine samples of all subjects. This reflects increased exposure to the parent materials of these metabolites. The median concentration of MBzP, MEHP, MEP, and MEP was recorded as 1.4, 54.5, 29.9, and 490 ng/ml, respectively. The lowest urinary concentrations were observed with MBzP. These findings are consistent with that of Jeddi et al. [29] who found that MBzP had the lowest levels in both unadjusted and creatinine-adjusted models with a geometric mean value equal to 2.0 μg/L. On the other hand, Bamai et al. [30] found that the median concentrations of MBzP and MEHP in children aged 3–12 years were 17.05 and 16.9 μg/L, respectively, while Amin et al. [31] reported that the median concentrations of MBzP and MEHP were 240.77 and 101.97 μg/L, respectively. The European Food Safety Authority attributed in 2011 the differences in the reported urinary metabolite patterns to differences of the used patterns of phthalates in related products, variations in food consumption habits, and/or variances in socio-economic levels in different countries [32].

Table 4: Correlation between phthalate metabolites and anthropometric measurements and biochemical indices

| BMI z-score category | Mean | Std. Deviation | t-test | p |
|----------------------|------|----------------|--------|---|
| Mono-(2-ethylhexyl) phthalate (ng/ml) | | | | |
| Obese | 65.9241 | 23.28435 | 3.979 | 0.000* |
| Non-obese | 53.6750 | 14.44615 | | |
| Monobenzyl (ng/ml) | | | | |
| Obese | 606.2759 | 272.06311 | 3.823 | 0.000* |
| Non-obese | 478.0570 | 136.72614 | | |
| Monobutyl (ng/ml) | | | | |
| Obese | 1.8642 | 0.87290 | 1.735 | 0.085 |
| Non-obese | 1.6368 | 0.71872 | | |
| Monobutyl (ng/ml) | | | | |
| Obese | 31.7084 | 6.27011 | 2.062 | 0.041* |
| Non-obese | 29.5349 | 6.24461 | | |

*p < 0.05 is significant.

Metabolic processes showed greater vulnerability to environmental agitations throughout periods of development, characterized by hormonal variations and quick maturation of organs [33]. It has been assumed that phthalate disrupts lipid metabolism by affecting various human receptors: Peroxisome proliferator-activated receptors (PPARα and PPARγ), human estrogen receptors, androgen receptors, thyroid hormone receptors, and pregnane X receptor [34].

The present study showed a positive significant correlation between urinary monobenzyl and serum triglycerides, and insignificant negative associations between MEHP, MEP, and total cholesterol and triglycerides. Triglyceridaemia correlated with phthalates exposure was evidenced in the previous studies [31, 34, 35]. In contrast, Jia et al. [36] reported that high serum MEHP was associated with lower triglycerides, as well as lower levels of several fatty acid components in 318 pregnant Japanese women. In addition, reduction of TG concentrations following MEP exposure was documented in non-obese [37]. Reduction in cholesterol levels was also recently reported among Mexican youth at 8–14 years of age [38]. Nevertheless, the effect of phthalate exposure on lipid profile is evidently more complicated. It was postulated that phthalate activation of PPARα may lead to hypolipidemic and antiadipogenic effects, while their activation of PPARγ may lead to pro-adipogenic effects [39].

It was hypothesized that phthalates exposures prenatally, in childhood, and through adolescence were related to increased weight status and adiposity [40, 41, 42, 43, 44]. In the present study, it was found that the mean urinary levels of MBP, MEP, and MEHP in children with obesity were higher with a highly significant difference if compared with that of non-obese children. In addition, positive significant correlations between both MEHP and MEP on one side and body weight, BMI-Z score, WC, and HC on the other side were noted. This agrees with other studies, where MBzP, MEHP, and MEP were correlated with WC and BMI [26, 40]. Khalil et al. [45] showed a positive association between urinary phthalates and BMI in overweight children. In Iranian children, the high levels of phthalates were detected in children and adolescents with obesity in associations with increased BMI and WC [31]. WC as a tool to evaluate visceral obesity was more informative than BMI. These indicators have an association with increased cardiometabolic risks [46]. Moreover, a positive linear correlation between WC and urinary MEHP concentrations was also found in healthy normal-weight individuals [37]. Furthermore, recent epidemiological research has supported phthalates' role in triggering adverse cardiometabolic states in children and adolescents [31, 47].

The potential mechanisms assumed in the association between phthalates and obesity may include endocrine-disrupting activities and activation of PPARs. Activation of these receptors can increase lipid accumulation [48] and release adiposity hormones, causing an increased risk for developing obesity [49].

On the contrary, increased levels of MEP and DEHP were reported in the serum and urine of people undergoing weight loss [50]. Another study had reported a
negative correlation between levels of urinary phthalates and weight gain in children [51]. Other studies have not found associations between phthalate exposure and adiposity [52], [53]. Inconsistencies among reports can be explained by differences in methodological approaches, as variances in periods of exposure and outcome assessments (e.g., pre-puberty vs. post-puberty), data analysis methods (for instance, sex-stratified vs. all subjects), and populations risk factors such as genetics, epigenetics, and other confounders.

The principal limitation of this study is that it is cross-sectional, and thus a causal relationship cannot be proven.

Conclusion and Recommendation

The present study supports that phthalates exposure can lead to an increase in children’s and adolescents’ body weight, adiposity, and triglycerides. Community efforts to restrain phthalates use should be encouraged. Upcoming studies have to shed light on the risk of phthalates exposure in children and its association with later obesity and cardiovascular wellbeing, besides exploring the probable underlying mechanisms and causation.

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