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The relationship between urinary bisphenol A levels and body weight in children

Bisphenol A levels and body weight

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Abstract
Aim: Bisphenol A (BPA), one of the most commonly produced and used endocrine disruptors in the world, is a chemical employed in the production of polycarbonate and epoxy resins. A significant relationship between urinary BPA levels and obesity has been shown in clinical trials. This study aimed to investigate the relationship between urinary BPA levels and obesity in childhood.
Material and Methods: The study was performed with a total of 172 children: 75 participants with a weight status of obesity, 33 participants with a weight status of overweight, and 64 participants with a weight status of normal. Sociodemographic data, family history of chronic diseases, preferred water/beverage/food containers, prepared water/beverage/food consumption, screen-based behavior time, and regular physical activity rates of children data were gathered from parents via questionnaire.
Results: Among 172 children, 47.7% (n = 82) were males and 52.3% (n = 90) were females. The mean age was 11.7 ±3.3 (4-18) years. The age and gender distribution was similar between the body mass index groups. The total screen-based sedentary behavior time was higher in the obese group than in the normal weight group; 85.6% (n = 143) of all participants drank water from plastic bottles. Socio-demographic and anthropometric features, total time of screen-based sedentary behaviors, usage of plastic water/beverage/food containers, pre-packaged water/beverage/food consumption, and IR detection rates were similar between the BPAmcg/kreat percentile groups.
Discussion: BPA was detectable in all urine specimens. As the urinary BPA level increased, BMI SDS increased. Urinary BPA levels were not associated with IR.

Keywords
Bisphenol A, Childhood, Insulin Resistance, Obesity

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Introduction

Obesity became an epidemic in the first decade of the 21st century. In 2010, forty-two million children below the age of five were overweight worldwide. Thirty-five million of these children were living in developed countries (available at: http://www.who.int/dietphysicalactivity/childhood/en/). Globally, the prevalence of overweight and obesity combined has risen by 47.1% for children between 1980 and 2013. [1]. Various industrial products, such as polymers known for their durability, are ubiquitous in the products of modern, developed countries. Unfortunately, it has been recognized in recent years that these products can be harmful. The effects of widely-used chemicals on the endocrine systems of humans have been increasingly investigated and understood.

Bisphenol A (BPA) is found in polycarbonate plastics and epoxy resins. Polycarbonate plastics are often used in containers that store food and beverages, such as water bottles. They are also used in many consumer goods [2]. Though BPA has been used since the 1970s, its effects have only recently been understood, with the first clinical studies published in the last decade. Until this research, no study investigating the relationship between BPA exposure and obesity in Turkish children had been published. The present study aimed to investigate the relationship between childhood obesity and urinary BPA levels.

Material and Methods

Study and control groups: Study participants included children diagnosed with overweight or obesity who were followed up between March 2014 and October 2014 at the Istanbul Faculty of Medicine, Pediatric Endocrinology outpatient clinic. The age-and gender-matched control group included children who presented to Istanbul Faculty of Medicine, General Pediatrics outpatient clinic with normal weight and no chronic disease or history of drug usage. All parents of the participants were informed of the study objectives. Written consent was obtained from all parents, and written or verbal consent was obtained from all children included in the study. The study was approved by the Ethics Committee of Istanbul University Faculty of Medicine (no. 1795). This study was funded by the Scientific Research Projects Coordination Unit of Istanbul University (project number: 41594).

Clinical evaluation: Height and weight of all subjects were measured by an experienced physician using a wall-mounted, calibrated Harpenden Stadiometer (Holtain Ltd., Crymych, UK) and an electronic scale (sensitivity at 0.1 kg level). Body mass index (BMI) was calculated using the following formula: BMI = weight (kg)/height (m2). Height and weight measurements of the parents who were present during outpatient follow-up visits were performed as well. Standard deviation scores (SDS) of these measurements were calculated using national data [3, 4]. The group classified as obese consisted of the children with BMI SDS >2. The group classified as overweight consisted of children with BMI SDS 1-2. The normal weight group consisted of the children with BMI SDS <1. The BMI values of the parents who were absent during outpatient follow-up were calculated with height and weight data based on parent declaration. BMI values between 25 and 30 classified subjects as overweight, while BMI values >30 classified subjects as obese.

A total of 178 patients were initially accepted to participate in the study. Two children in the normal weight group were later excluded from the study due to malnutrition, and two children in the obese group were excluded from the study because their urine samples became unusable either some other time during the study. The study continued with a total of 172 patients, including 75 patients with obesity, 33 patients with overweight, and 64 patients with normal weight.

Laboratory evaluation and biochemical assays: Fasting glucose, fasting insulin, and blood lipid profile values of the participants were obtained from the laboratory result system. Insulin resistance was evaluated with the homeostasis model assessment for the insulin resistance index (HOMA-IR), which was calculated as insulin (mU/l) × (glucose [mg/dl] × 0.055)/22.5 (HOMA-IR). HOMA-IR limit values in the prepubertal period were 2.67 in boys and 2.22 in girls. In the puberty period, these limit values were 5.22 in boys and 3.82 in girls. When evaluating blood lipid levels, total cholesterol levels of >213 mg/dl, HDL cholesterol levels of <33 mg/dl, LDL cholesterol levels of >135 mg/dl, and triglyceride cholesterol levels of >195 mg/dl were considered abnormal [5,6].

Fresh spot urine samples were obtained from all children and placed in glass urine containers. The urine samples were kept at -20 Co until the time of the study. BPA, bisphenol A glucuronide (BPAG), and creatinine levels were measured in urine samples using high-performance liquid chromatography/mass spectrometer method. Since spot urine was obtained, the results were corrected by dividing them by urinary creatinine value. The total numbers of corrected and uncorrected BPA and BPAG values were evaluated [7]. Percentile ranges were determined by BPA levels, and the patients were divided into four groups accordingly.

The laboratory method used in this study, reported in the research conducted by Battal et al., is a newly developed method. This method has been standardized and its sensitivity and validity have been proven. It was developed to obtain a more sensitive measurement for BPA and BPA glucuronide (lower limit for detection BPA:0.03 µg /L, BPA glucronide:0.10 µg /L) [9]. The high percentage of BPA detection may also be explained by the difference in the laboratory method.

Statistical analysis

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) was used for statistical analysis. When evaluating the study data, the Welch ANOVA test was used for comparison between three or more groups in terms of variables that showed a normal distribution in comparison of quantitative data, and the Games-Howell test was used to determine the group that caused the difference. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were also used. The Kruskal-Wallis test was used to compare three or more groups that did not show a normal distribution, and the Mann-Whitney U test was used to determine the group that caused the difference. Pearson's chi-square test and the Fisher-Freeman-Halton exact test were used in the comparison of qualitative data. A p-value of < 0.05 was considered significant.

Results

Among 172 children, 47.7% (n = 82) were males and 52.3% (n = 90) were females. The mean age was 11.68 ±3.25 years (4-18 years). The age and gender distribution between the groups was statistically similar. Familial obesity rates were lower in the subjects with normal weight than in the subjects with overweight or obesity. Comparison of gender, age, height, weight, and parental obesity history in the groups is shown in Table 1.

Evaluation of insulin resistance and dyslipidemia: Fasting blood glucose (FBG) levels were significantly higher in subjects with normal weight compared to subjects with obesity and overweight. Besides, fasting insulin values were higher in the subjects with obesity compared to the subjects with normal weight. HOMA-IR values were higher in the obesity group compared to the normal weight group. Comparison of glucose and lipid metabolism parameters between the groups is shown in Table 2.

Evaluation of the total of the urine creatinine-corrected BPA and BPAG measurements: The mean values of urine creatinine-corrected BPA and BPAG measurements increased in proportion with BMI, but no difference was observed between the median values that were used in statistical assessment, since there was no normal distribution (Table 3).

Table 1. Comparison of the gender, age, anthropometric measurements, and parental obesity history in the groups

		Total (n=172)	Obese (n=75)	Overweight (n=33)	Normal weight (n=64)	P
Gender n(%)	Male	82 (47.7)	33 (44.0)	19 (57.6)	30 (46.9)	0.423
	Female	90 (52.3)	42 (56.0)	14 (42.4)	34 (53.1)	
Age (years) (mean±SD)		11.68 ±3.25	12.01 ±3.15	11.64 ±3.43	11.31 ±3.29	0.447
Weight SDS		2.95 (5.02-1.15)	-0.16 (-2.36-1.99)	0.001	1.68 (-2.25-2.93)	0.001
Height SDS		0.73 (-3.13-4.01)	-0.01 (-2.97-3.85)	0.014	0.60 (-3.4-3.54)	>0.05
BMI SDS		2.73 (2.00-4.05)	-0.12 (-2.02 -1.00)	0.001	1.68 (1.12-1.98)	0.001
Presence of obesity in the family		128 (74.4)	60 (80.0)	25 (75.8)	43 (67.2)	0.001
1.st degree relative		99 (57.6)	43 (57.3)	17 (51.6)	39 (60.9)	0.001
2.nd degree relative		69 (40.1)	39 (52.0)	13 (39.4)	17 (26.6)	0.004

Table 2. Comparison of glucose and lipid metabolism between the groups

	Obese (n=75)	Normal weight (n=64)	p1	Overweight (n=33)	p2
FGL (mg/dL)	89 (70-119)	93 (71-142)	0.001**	87 (75-102)	0.011*
Insulin	16.65 (4.4-53.8)	9.40 (4-27.9)	0.003**	12 (7,9-29,4)	>0.05
HOMA-IR	3.58 (0.89-11.92)	2.31 (0,96-7.78)	0.014*	2,40 (1,56-6,32)	>0.05
Triglyceride(mg/dL)	105 (41-324)	55 (29-126)	0.001**	82 (39-148)	0.011*
Cholesterol(mg/dL)	161 (90-273)	147 (83-215)	0.014*	159 (134-196)	0.047*
HDL (mg/dL)	45 (22-70)	47.50 (39-62)	>0.05	49 (42-65)	>0.05
LDL (mg/dL)	95 (41-196)	82.50 (15-151)	>0.05	93 (66-131)	>0.05

*p<0,05 **p<0,01, p1 value belongs to the comparison of the obese subjects and the subjects with normal weight, p2 value belongs to the comparison of the overweight subjects and the subjects with normal weight.

Table 3. Distribution of total urinary BPA levels according to the BMI SDS groups

	Total (n=172)	Obese (n=75)	Overweight (n=33)	Normal weight (n=64)	P
BPAµg/g crea	55.6 (8.7-1331.7)	67.1 (8.7-1331.7)	43.9 (12.8-941.8)	54.1 (14.6- 651.4)	0.521

Median (min-max) values are given because of the abnormal distribution of BPA.
BPA: Bisphenol A, BMI: Body mass index, SDS: Standard deviation score

Discussion

Obesity occurs due to a combination of genetic, behavioral, and environmental factors [9]. Industrialization in the food sector, a reduction in physical activity, and increased calorie intake as a result of rapidly developing technology are the main causes of obesity. BPA is an endocrine disrupter chemical, and is widely used to produce polycarbonate and epoxy resin all over the world [9]. BPA is frequently used in packages of water, beverages, and food. Consumption of these products is thought to be the main reason for BPA exposure. BPA exposure is determined by measuring BPA levels in urine. A few multiparticipant research indicated that BPA had been found at rates in urine samples in the range from 83% to 98% [10-12].

In this study, BPA was detected in all urine samples. The study group consisted of a limited number of subjects, including individuals with obesity and overweight, and a control group, which is likely the main reason for the increased rate of BPA detection. Another potential cause of high BPA rates is that spring water throughout Turkey, and particularly Istanbul, is commonly kept, sold, and consumed in bottles and carboys containing BPA.

The results of this study were also compared with data from clinical studies conducted with children in the literature. In the study conducted by Becker et al., the 50th percentile value for urinary BPA was 2.81 µg /L for the 6-8 year age group, 2.13 µg /L for the 9-11 year age group and 2.6 µg /L for the 12-14 year age group [12]. In the study conducted by Calafat et al., the percentile distributions of urinary BPA values by age were examined according to the NHANES 2003-2004 data. In the 6-11 year age group, the 50th percentile value for urinary BPA was 3.7 µg /L, and the 95th percentile value was 16 µg /L. In the 12-19 year age group, the 50th percentile value for urinary BPA was 4.2 µg /L, and the 95th percentile value was 16.5 µg /L. In the 6-11 year age group, the 50th percentile value for urine creatinine corrected BPA was calculated as 4.2 µg/g creatinine, and the 95th percentile value was calculated as 15.7 µg/g creatinine. In the 12-19 year age group, the 50th percentile value was calculated as 2.7 µg/g creatinine, and the 95th percentile value was calculated as 11.4 µg/g creatinine [11]. The results of these two studies, conducted at the national level, were higher than those found in this study. In this study, in which the subjects were between the ages of 4 and 18, the 50th percentile value for creatinine-corrected urinary BPA was 0.056 µg/g creatinine. The difference in age ranges and number of subjects between the studies might have caused the difference in results.

In the studies conducted by Transande and Wells, an increase in the prevalence of obesity was found with increasing BPA percentile [13, 14]. In our study, a gradually increasing percentage in the total prevalence of obesity and overweight with increasing BPA percentile in the groups established by the percentile ranges of urine creatinine-corrected BPA values. When the prevalence of obesity was examined alone, an uptrend was noted in the 1st, 2nd, and 3rd groups (59.5% in the first group, 67.4% in the 2nd group, 69.8% in the 3rd group). Again, a gradually increasing percentage in the prevalence of overweight and obesity corresponded with increasing BPA percentile in the groups established by non-urine creatinine-corrected BPA values percentile range (36.4% in the 2nd group, 40.5% in the 3rd group, 53.5% in the 4th group). These findings suggest that increased urinary BPA values are associated with an increased prevalence of overweight and obesity.

In a study conducted in China by Wang et al., an increase in the prevalence of obesity was found with increasing BPA percentile in the 8-11 year age group and in girls [10]. In another study conducted in China by Li et al., 2 ng/ml was considered the limit value, and increased BPA value was associated with obesity in prepubertal girls (9-12 years). This association was not observed in boys or in the total population, however [15]. In this study, a no correlation was found between BPA levels and prevalence of obesity in comparisons made with age and gender.

Eng et al. considered the consumption of instant drinks at least once a day a risk factor for increasing BPA due to BPA in the packages, as well as a risk factor for obesity because of increased calories intake [16]. However, in their study, they did not find a significant correlation between BPA levels and consumption of instant drinks. No correlation was found between BPA percentile and the variables for insulin resistance and fasting blood glucose [16]. In our study, the number of subjects with insulin resistance increased with increasing BPA presence, though it was not statistically significant. In a study conducted by Khalil et al., fasting insulin and increased HOMA-IR were correlated with an increased presence of BPA in men [17]. These findings may be explained by the effects of BPA on insulin release.

Some methodological differences render comparison of the studies difficult. Urinary BPA level has been corrected with urine creatinine in most studies. However, in some studies, such as in a study conducted by Wang et al., urinary BPA has been corrected with urine density. Creatinine level varies with the amount of muscle mass and by gender, such that corrections made with urine creatinine may further decrease the values in men. Urinary density is a highly variable parameter. Assessment considering the urinary creatinine ratio is a commonly used method in drug studies. There is no consensus on the ideal method for BPA correction. This makes it difficult to compare values. Since BPA level has been corrected with urine creatinine in most studies conducted with children, this study used that method. Another methodological difference is related to the BPA measurement technique. Although the method used in this study is similar, it is thought to be more sensitive [7]. However, this method does not create a difference which could affect the results, because the standardization studies of the method are compatible with the global literature, and the minimum detectable concentration corresponds to the other studies. This sensitivity might have caused the detection of BPA in all samples, a result, which has not previously been found in the literature. Nevertheless, environmental contamination cannot be excluded.

The possibility that BPA, a lipophilic chemical, may accumulate in the adipose tissue is an unclear assumption. The relationship of BPA with BMI may be due to the accumulation of BPA at higher levels in individuals with obesity given excess adipose tissue. Thus, this finding may not be a cause, but rather an outcome [18]. The effect assigned to BPA may be the cumulative effect of many chemical substances. There are more than a thousand commercial chemicals that may have similar effects. These include bisphenol F and bisphenol S, which are being used with increasing frequency, and phenols and phytates, which have been introduced previously [19]. Products containing BPA may also contain other endocrine disrupters, and the effects attributed to BPA may be the effects of these chemicals or a cumulative effect. However, cell and animal studies that have observed the effects of BPA alone given in repeated doses, provide evidence supporting the effects of BPA.

Conclusion

This study found that screen-based behavior time increased the frequency of obesity and overweight. Physical activity rate was also higher in normal weight children than in children with obesity, which supports the association of physical activity with BMI. Obesity is a risk factor for IR and lipid profile abnormalities. Since urine creatinine-corrected BPA and BPGA increased in proportion with BMI, exposure to BPA and obesity were thus correlated. In addition, BPA was correlated with IR. The contribution of BPA to obesity and IR was presented in this study, but more comprehensive research is needed in this area.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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