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Original Article

BPA exposure is related to metabolic changes in obese Saudi children

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Abstract: Background and objective: Bisphenol A (BPA) disturbs the metabolism in animals and humans through effecting endocrine system. The role of BPA in obesity is not studied well. Therefore, current study is conducted to investigate its association with childhood obesity. Methods: Using gas chromatography-mass spectrometry (GC-MS/MS) serum BPA level was measured in 177 (120 normal and 57 obese) Saudi children. Results: The analyses of the data revealed an elevated level of serum BPA, leptin, systolic blood pressure, triglyceride, insulin and vitamin D in obese children as compare to normal controls. An elevated serum BPA did not show association with increased vitamin D and insulin while positively associated with some of the key markers of obesity. BPA was also positively associated with laptin, insulin and diastolic blood pressure in individuals of both normal and obese groups but with little statistical differences. Conclusion: Higher BPA level in obese children reveals that it may involve in the childhood obesity as it has shown a significant association with the key makers of the obesity in obese children especially in boys.

Keywords: BPA, obesity, Saudi children

Introduction

In last decade, it has been hypothesized that some anthropogenic chemicals act as obesogenic [1-3] thus there are major concerns regarding chemicals that may act as endocrine disrupters. Bisphenol-A (BPA) is an endocrine disrupting chemical (EDC) used extensively in the plastics industry, such as polycarbonate plastics, plastic packaging and water bottles [4, 5]. Most of the people worldwide have detectable levels of BPA in their blood or urine indicating a ubiquitous exposure [6, 7]. Furthermore, BPA induces obesity in rodents in experimental settings [8, 9]. In humans urinary BPA is found to be related with obesity in adult boys and girls [10-13] but biochemical role of BPA in adulthood obesity is still needs to be investigated. Plastic products are extensively used in Saudi Arabia and obesity is also high. The prevalence of obesity has been increasing to an alarming rate. It has been observed that the prevalence of overweight and obesity among primary school male and female students is 7.3% and 17.4% and 12.4% and 20.9% respectively. Among Saudi regions the primary school students in Tabuk are 9.7% overweight and 19% obese [14]. Moreover, the prevalence of obesity in Saudi adolescent boys is significantly higher than the girls [15].

To the best of our knowledge the exposure of BPA and its association with childhood obesity study has never been reported anywhere in the world. Therefore, keeping in mind the role of BPA in obesity, the current study was performed to evaluate its association with childhood obesity in Saudi population. Gender based analysis of its association was also investigated and further we hypothesized that the association of BPA with obesity varies in boys and girls.

Materials and methods

Study population

A total of 177 Saudi children (57 obese and 120 non-obese, age 13-16 years old) were recruited from different public and private

schools in Riyadh, Saudi Arabia. For conducting this research an ethical approval was obtained from Ethics Committee of the College of Science Research Center, King Saud University, Riyadh, Saudi Arabia. Permission was also obtained from the Ministry of Education and the principals of the selected schools. Informed written consents were taken from the parents and the participants of the study.

Anthropometrics

Anthropometrics were done at different times according to the break hours of the students. Physical examination was carried out by the attending school physician and nurse to determine whether the participants fulfil the inclusion criteria. Weight and height of the participants were recorded using an appropriate international standard scale (Digital Pearson Scale, ADAM Equipment Inc., USA). Waist, hip and arm circumferences were measured by a non-stretchable tape. Blood pressure was measured twice with an interval of 15 minutes using standardized mercury sphygmomanometer. The mean systolic and diastolic blood pressure of two measurements was noted. The general and central obesity was measured using BMI and waist circumference, respectively.

Cut-offs

The cutoffs for age specific and gender based overweight and obesity were used as proposed for adolescents by Cole and colleagues [16]. Cut-offs for pediatric subjects from the IDF diagnosis of metabolic syndrome was used for LDL-cholesterol, fasting blood glucose and triglycerides [17].

Blood sampling and biochemical assessments

The individuals who fulfilled the inclusion criteria were asked to complete the questionnaire and advised to return school's clinic on the following day without having breakfast for blood withdrawal. 3-5 cc blood samples were collected and centrifuged on site to isolate serum and delivered immediately to Prince Mutaib Chair for Biomarkers of Osteoporosis (PMCO), Biochemistry Department, King Saud University in Riyadh, Saudi Arabia, for storage and analysis. Fasting blood glucose and lipid profile were measured as a routine analysis. Serum 25-hydroxyvitamin D was measured using COBAS e-411 automated analyzer (Roche Diagnostics, Indianapolis, IN, USA) in a DEQAS-certified laboratory (PMCO). For serum 25-hydroxyvitamin D assay, the inter- and intra-assay coefficients of variation (CV) were 8.0% and 5.6%, respectively, with a lower detection limit (LOD) of < 4 ng/ml).

Serum BPA concentration

BPA concentration level in serum samples (0.3 ml) was measured by gas chromatography coupled with mass spectrometry detector (GC-MS/MS) [18]. The limit of detection (LOD) was 0.1 ng mL-1 based upon a lower calibration standard (0.3 ng mL-1) which gave an instrument signal to noise response of 3:1. The quality control analysis was maintained by analyzing a method blank (serum) and two spiked serum samples 10 ng mL-1, after every 15 samples run in the GC-MS/MS system. Serum BPA was detected in 174 (98%) of the total 177 analyzed samples.

Statistical analysis

Data were analyzed using SPSS (version 22, Chicago, IL, USA) and continuous data were presented as mean ± standard deviation (SD), the gaussian variables and non-gaussian variables were presented in median (1^{st} and 3^{rd}) percentiles. Categorical data were presented as frequencies and percentages (%). All continuous variables were checked for normality using Kolmogorov-Smirnov test, if did not find normal then Non Gaussian variables transform to log & square root transformation. Independent t test was applied to check mean difference in Gaussian variables while Mann Whitney-U test was used for non-Gaussian variables. Relations among variables were sought by Spearman's & Pearson correlation coefficient for Gaussian and non-Gaussian variables. *P*-value < 0.05 was considered statistically significant.

Results

Total 57 obese children were investigated for association of serum BPA with the obesity markers and data obtained were compared with 120 ethnically and age matched non-obese controls collected from general population of Riyadh. Different parameters were studied including BMI, waist, hips, SBP, DBP, total cholesterol, glucose, HDL-cholesterol, LDL-cholesterol, triglycerides, insulin, leptin, and BPA.

Table 1. General characterization of subjects included in this study

Parameter	Normal	Obesity	*P*-Value	*P*-value*
N (Boys/girls)	120 (51/69)	57 (29/28)		
Age (years)	14.25 ± 1.89	14.7 ± 1.28	0.705	---
Body Mass Index (kg/m^2)	19.36 ± 2.50	27.88 ± 3.99	< 0.001	---
Waist circumference (cm)	73.56 ± 10.07	90.42 ± 10.45	< 0.001	0.779
Hip circumference (cm)	89.29 ± 8.20	106.91 ± 9.16	< 0.001	0.849
WHR	0.82 ± 0.08	0.86 ± 0.08	0.006	0.499
Systolic Blood Pressure (mmHg)	113.03 ± 15.9	119.9 ± 16.7	0.012	0.496
Diastolic Blood Pressure (mmHg)	71.17 ± 12.02	70.38 ± 11.85	0.687	0.836
Total Cholesterol (mmol/l)	4.65 ± 0.90	4.82 ± 0.73	0.232	0.180
Glucose (mmol/l)	5.11 ± 0.56	5.21 ± 0.63	0.297	0.236
HDL-Cholesterol (mmol/l)	1.16 ± 0.24	1.08 ± 0.22	0.032	0.739
LDL-Cholesterol (mmol/l)	3.03 ± 0.74	3.22 ± 0.59	0.104	0.126
Triglyceride (mmol/l)#	0.85 (0.63-1.16)	1.03 (0.81-1.29)	0.008	0.564
25 (OH) Vitamin D (nmol/l)#	24.1 (18.7-32.5)	24.2 (18.2-31.2)	0.414	0.240
BPA (ng/ml)#	1.89 (1.32-2.62)	1.65 (1.07-2.44)	0.184	0.840
Insulin (pg/ml)#	516.69 ± 210.44	606.65 ± 281.46	0.187	0.085
Leptin (ng/ml)#	10.25 (3.75-20.9	16.72 (13.20-45.42)	< 0.001	0.164

Note: Data presented as mean ± standard deviation & median (25th -75th) percentile for Non Gaussian variables (# represent non Gaussian); *P*-Value denotes significance at < 0.05 and 0.01 level. *indicates *P*-values adjusted for age, gender and BMI.

Table 2. Gender based analysis on effect of BPA on obesity and its markers

Parameter	Boys		*P*-Value	Girls		*P*-Value
	Normal	Obese		Normal	Obese	
N	51 (63.8)	29 (36.3)		69 (71.1)	28 (28.9)	
Age (years)	13.9 ± 0.9	14.0 ± 1.0	0.588	14.5 ± 1.3	14.4 ± 1.5	0.594
Body Mass Index (kg/m2)	18.9 ± 2.4	28.0 ± 4.1	< 0.001	19.8 ± 2.5	27.8 ± 4.0	< 0.001
Waist circumference (cm)	73.8 ± 6.5	93.9 ± 9.5	< 0.001	73.5 ± 11.4	88.2 ± 10.6	< 0.001
Hip circumference (cm)	85.7 ± 6.9	105.8 ± 9.8	< 0.001	91.0 ± 8.2	107.6 ± 8.8	< 0.001
WHR	0.9 ± 0.1	0. 9 ± 0.1	0.045	0.8 ± 0.1	0.8 ± 0.1	0.038
Systolic Blood Pressure (mmHg)	119.5 ± 15.0	125.9 ± 14.4	0.025	108.2 ± 14.9	112.9 ± 15.9	0.178
Diastolic Blood Pressure (mmHg)	73.8 ± 14.1	69.4 ± 11.9	0.171	69.2 ± 9.8	71.4 ± 11.9	0.363
Total Cholesterol (mmol/l)	4.5 ± 0.9	4.7 ± 0.7	0.122	4.8 ± 0.9	4.9 ± 0.8	0.619
Glucose (mmol/l)	5.3 ± 0.5	5.3 ± 0.5	0.723	5.0 ± 0.6	5.2 ± 0.7	0.209
HDL-Cholesterol (mmol/l)	1.1 ± 0.2	1.1 ± 0.3	0.882	1.2 ± 0.3	1.0 ± 0.2	0.005
LDL-Cholesterol (mmol/l)	2.9 ± 0.8	3.2 ± 0.5	0.045	3.1 ± 0.7	3.2 ± 0.7	0.525
Triglyceride (mmol/l)#	0.8 ± 0.3	1.1 ± 0.4	0.011	0.9 ± 0.3	1.2 ± 0.5	0.011
25 (OH) Vitamin D (nmol/l)	35.4 ± 13.3	28.2 ± 11.1	0.028	21.7 ± 7.5	23.1 ± 7.8	0.445
BPA (ng/ml)#	2.4 (1.6-3.4)	1.9 (1.3-2.8)	0.249	1.6 (1.2-2.2)	1.4 (1.0-1.8)	0.155
Insulin (pg/ml)	377.5 ± 83.1	445.8 ± 175.2	0.294	613.1 ± 218.8	745.9 ± 209.2	0.187
Leptin (ng/ml)#	3.4 (1.5-8.7)	13.5 (11.7-18.4)	< 0.001	16.2 (8.6-23.7)	54.7 (18.4-62.9)	< 0.001

Note: Data presented as mean ± standard deviation & median (25th -75th) percentile for Non Gaussian variables; # indicates non-normal variables; *P*-Value denotes significance at < 0.05 and 0.01 level.

The obesity related biochemical markers were significantly higher in obese children than the normal controls. Thus, as compared to non-obese controls, obese have significantly higher level of BMI (19.36 ± 2.50 vs. 27.88 ± 3.99 kg/m^2, P ≤ 0.001), Waist (73.56 ± 10.07 vs. 90.42 ± 10.45 cm, P ≤ 0.001), circumference (89.29 ± 8.20 vs. 106.91 ± 9.16 cm, P ≤ 0.001), SBP (113.03 ± 15.87 vs. 119.39 ± 16.37 mmHg, P = 0.016), HDL-cholesterol (1.16 ± 0.24 vs. 1.08 ± 0.22 mmol/l, P = 0.032), Triglyceride (0.85 (0.63-1.16) vs. 1.03 (0.81-1.29) mmol/l, P =

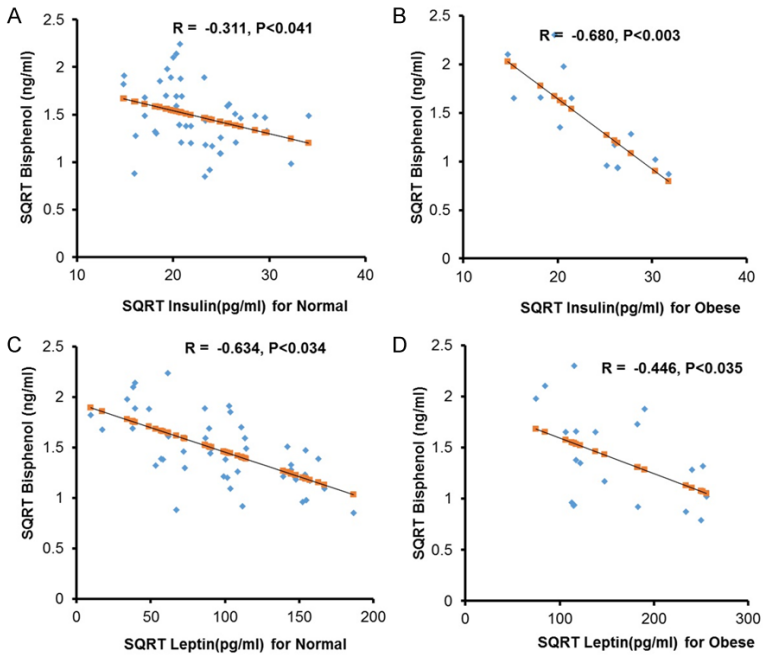

Figure 1. Association of Bisphenol with Leptin and Insulin. (A) Showing negative correlation between BPA and Insulin in normal controls. (B) Showing strong negative correlation between BPA and Insulin in obese children. (C) BPA is negatively associated with Leptin in normal controls and (D) Obese children.

0.008), and leptin (10.25 (3.75-20.9) vs. 16.72 (13.20-45.42) ng/ml, P ≤ 0.001) for healthy and obese children, respectively **Table 1**.

Further, we studied sex based differences; obese boys have significantly higher systolic blood pressure (P = 0.025), LDL-cholesterol (P = 0.045) and leptin (P ≤ 0.001) than the healthy boys while obese girls have significantly higher levels of HDL-cholesterol (P < 0.05) and leptin (P ≤ 0.001) than the healthy girls (P ≤ 0.001) **Table 2**.

We performed correlation analyses of BPA with other parameters in obese and normal children which revealed a significant (P < 0.05) association with BMI (-0.230), systolic blood pressure (SBP) (0.234), insulin (-0.311) and leptin (-0.634) in normal children. The analysis of obese children showed that BPA positively correlated with Hip (0.317), while negatively insulin (-0.755) and leptin (-0.446) (**Figure 1**). Gender based analyses showed, WHR (-0.417), SBP (-0.517), glucose (-0.364) and 25OH-vitaminD (-0.398) has significant (P < 0.05) correlation in normal boys while on the other hand total cholesterol (0.315) and LDL-cholesterol (0.278) showed significant correlation with normal girls. Glucose (-0.405) and insulin (-0.680) showed significant negative correlation in obese boys while LDL-cholesterol showed significant correlation with obesity in girls (0.408) **Table 3**.

Discussion

Childhood obesity is an epidemic worldwide, both in advanced and developing countries. The underlying mechanisms causing obesity are not fully understood yet but it is believed as multifactorial disorder including age, sex, lifestyles and environmental factor such as pollutants exposure etc. Exposure to endocrine disruptors not only increases the risk of metabolic and cardiovascular diseases (CVD) but it has also been associated with the obesity. In addition to lifestyle and environmental factors, chemicals agents acting as endocrine disruptors may cause childhood obesity [19]. Several studies have confirmed that the exposure to BPA increases body weight and adiposity [20-22]. Few studies have examined the association of urinary BPA and obesity in humans [11, 23, 24], while recently a study has showed the association between exposure to BPA with cardio metabolic and obesity in children [25]. To best of our knowledge, no other similar studies have been conducted so far on the association between serum BPA level and childhood obesity. As it is well known that BPA act as endocrine disrupting agent and also effect the metabolism in human and other animals. Therefore, we believe that BPA must have association with obesity or its associated factors.

Hence, in current study we examined the exposure and association of serum BPA concentrations with childhood obesity in 177 children from Saudi Arabia (57 Obese and 120 non-obese control subjects). The results of the study showed a higher serum BPA concentration in overweight and obese. Serum BPA level

Table 3. Correlation between BPA level and biochemical parameters

Parameter	Normal			Obesity		
	93 (Boys/girls)			57 (Boys/girls)		
	All	Boys	Girls	All	Boys	Girls
N	120	51	69	57	29	28
Age (years)	0.032	0.174	0.172	-0.047	-0.105	0.142
Body Mass Index (kg/m^2)	-0.230**	-0.226	-0.162	0.108	0.181	0.009
Waist circumference (cm)	-0.108	-0.261	-0.070	0.172	0.120	0.126
Hip circumference (cm)	-0.155	0.034	-0.192	0.107	0.020	0.187
WHR	0.029	-0.417*	0.138	0.317*	0.166	0.350
Systolic Blood Pressure (mmHg)	0.234**	0.517**	-0.234	0.087	0.160	-0.353
Diastolic Blood Pressure (mmHg)	0.127	0.040	0.106	0.084	0.032	0.276
Total Cholesterol (mmol/l)	0.013	-0.060	0.315*	0.034	-0.187	0.360
Glucose (mmol/l)	-0.031	-0.364**	0.073	-0.117	-0.405*	0.156
HDL-Cholesterol (mmol/l)	-0.007	0.171	0.037	-0.015	-0.119	0.155
LDL-Cholesterol (mmol/l)	-0.043	-0.156	0.278*	0.104	-0.125	0.408*
Triglyceride (mmol/l)#	-0.041	0.046	0.009	-0.089	-0.135	0.059
25 (OH) Vitamin D (nmol/l)#	0.025	-0.398**	0.151	-0.050	-0.333	0.149
Insulin (pg/ml)#	-0.311*	0.136	0.271	-0.755**	-0.680**	-0.735
Leptin (pg/ml)#	-0.634*	-0.335	-0.353	-0.446*	-0.014	-0.116

Note: Data presented as coefficient (R); *denotes significance at 0.05 level; **denotes significance at 0.01 level; #denotes Non Gaussian variables.

was significantly associated with increasing LDL-cholesterol in girls only, while in boys the level of BPA decreased with glucose and insulin levels. These results are suggestive that BPA exposure in children, can lead to adverse metabolic effects and high systolic blood pressure. The mean serum BPA concentrations in the obese children was in average 2.24 ng/ml range (1.45 to 3.01 ng/ml), as compared to 4.4 ng/ml reported in US population based sample of children aged 6-19 years in 2009-2010 NHANES [26]. In the current study, results showed significant associations with several metabolic outcomes even at comparatively lower BPA concentrations.

Our results indicated that there is a negative correlation between BPA level and insulin levels, in both obese and normal control children, respectively. This relation reflects clearly and confirms that BPA can affect insulin secretion and this association could be explained by the ability of BPA to increase [27]. A similar trend was observed by Ropero et al [28]. They suggested that the BPA can exert effects on the insulin-secreting beta cells, as well as on the glucagon-secreting alpha cells of the pancreas. Furthermore, they reported that exposure of male mice to BPA for 4 days leads to hyperinsulinemia and then to insulin resistance [28, 29].

An early study reported that the exposure to a chemical pollutants can cause obesity in women [30] BPA exposure may have effects on body weight. Sex- and dose- dependent differences in body weight in response to early postnatal exposure to DES, an estrogenic compound with structural similarities to BPA have been reported [31]. The evidences of relations between BPA level and obesity in human are not much frequently available. various studies have reported an association between environmental chemicals exposure and the development of obesity [1, 32-35] Mechanistic studies suggested that the disruptive effects of endocrine disrupting chemicals are exerted on adipocyte development [36, 37]. In current study serum leptin level increased in both obese boys and girls but girls have significantly higher level; overall increased level of BPA has been associated with the increase in Leptin level. This is consistent with results of an experimental study conducted by Wei et al. in which leptin levels were increased in perinatal BPA-treated offspring [38]. On the other hand, serum leptin levels in mice were lower in the female offspring of dams exposed to BPA than in the offspring of control dams [39].

The main strengths of our study include its representation of young children and the availabil-

ity of extensive data on metabolic and hormonal profiles of the candidates. To the best of our knowledge, this is the first ever report on an association between BPA exposure-response with metabolic and hormonal changes in obese Saudi children. However, there is a limitation i.e. this is the small sample size for a robust statistical analysis. Further, a study on a larger sample size with robust statistical analysis is recommended.

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Disclosure of conflict of interest

None.

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