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Research Article

The Impact of Bisphenol A (BPA) As Environmental Obesogen on Lipids and Lipids Metabolism

Fateheya M Metwally[1*], Magdy M Mohamed[2], Sharaf N E[1], Mohamed A Ghazy[2], El Mishad A M[1], Asmaa Elfiky[1]

[1]*Occupational and Environmental Medicine Department, Environmental Research Division, National Research Centre, Cairo, Egypt.*
[2]*Biochemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt.*

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ABSTRACT
Bisphenol A (BPA) is a monomer of polycarbonate plastics and is a ubiquitous responsible for environmental chemical pollutant and can migrate from polymers to food or water. It is considered as an environmental obesogenic through promoting adipogenesis, lipid accumulation and endocrinal disrupting chemicals (EDCs) altering adipokine hormone release. The aim of this study was to assess the impact of BPA on lipid metabolism and its profile. This work included 85 females aging from 16 To 58 years, after application of exclusion criteria. Among them 48 females with BMI ≥ 25 kg/m^2 (Gr-A) and 37 females with BMI< 25 kg/m^2 (Gr-B). All participants were subjected to detailed questionnaire and a clinical examination, sBPA, adiponectin, leptin hormones and lipid profile were assessed for all subjects. Results showed that the level of BPA was higher in (Gr-A) compared to (Gr-B). A significantly high levels of leptin, cholesterol and LDL-c (p < 0.001) were recorded with significantly low levels of adiponectin (p < 0.001) & HDL-c (p<0.05) in (Gr-A) compared with those of (Gr-B). There was a positively significant correlation between BMI & BPA, cholesterol, LDL-c, and leptin while a negative one between BMI and adiponectin, HDL-c. If studied population was divided according to their BPA concentration, the adiponectin was significantly lower in Gr I of high BPA concentration. However, adiponectin showed a non-linear relationship across different BPA concentration. In conclusion, this study showed that BPA is closely linked to obesity, in other words, it caused increasing in BMI via affecting the hormones responsible for lipid metabolism resulting in alteration of lipid profile.

Keywords:

INTRODUCTION

BPA is a small molecule~(228 Da) , used as a monomer in the polymerization reaction to manufacture polycarbonate plastics. Polycarbonates are used in numerous consumer products, including food and water containers, baby bottles, lining of food and beverage metal cans, medical tubing, epoxy resins, dental fillings and household electronics[1-3]. It can migrate from polymers to food or water, especially when heated[4]. The main route for exposure of the general population to bisphenol A is by ingestion of contaminated food and water[5,6], dermal exposure continues to increase, while inhalation of polluted air is being limited[7]. It is also proved to be an environmental obesogen altering energy balance, promoting adipogenesis and lipid accumulation[8], leading to increased BMI and waist circumference[9,10], resulting in both general and central obesity BPA act as a hormonal disruptor, disrupting many hormones likes adiponectin and leptin that are regulate the energy intake in the long term[11-14], causing alteration of several metabolic functions[15-17]. BPA can mimic endogenous hormones, subsequently disturb endocrine function[18,19]. BPA has a strong binding affinity for the transmembrane estrogen receptor (ER), G-protein-coupled receptor 30 (GPR30), and estrogen-related receptor (ERR)[20,21]. it can activate transcription factors, such as peroxisome proliferator-activated receptors PPARs) and the aryl hydrocarbon receptor (AhR)[22,23]. Rustling in BPA may influence normal differentiation and maturation processes during embryonic and fetal development, predisposing individuals to chronic disease, such as obesity, throughout the life span[24,25]. Furthermore, *In Vitro* studies of 3T3-L1 cells, revealed that BPA increased lipoprotein lipas(LPL) activity and triacylglycerol accumulation resulted in the presence of larger lipid droplets in the differentiated cells[26].The aim of this study is to assess the impact of BPA on lipid metabolism and lipid profile

SUBJECT AND METHODS

Study population

This work included eighty five females; they were recruited from the clinic of the National Research Centre in Dokki, Cairo, Egypt. Fourty eight females aging (35. 8± 10.9) were suffering from various grades of obesity, with BMI ≥ 25, (Gr A). Thirty seven females aging (34.2±10.2) matched for age, sex, socioeconomic status and smoking

**Author for Correspondence:*

Table 1: General characteristics of the study groups.

Variables	Gr A BMI≥ 25 n=48	Gr B BMI< 25 n=37	p-value
	Mean ±SD	Mean ±SD	
Age (years)	35. 8± 10.9	34.2±10.2	>0.05
Weight (Kg)	87.6±16.2	57.7±6.8	< 0.001**
Height (cm)	161.6±5.3	161.4±4.01	>0.05
BMI (Kg/m2)	33.4±6.1	22.1±2.3	< 0.001**
Waist circumference WC (cm)	95.4±13.3	73.8±7.9	< 0.001**
Systolic blood pressure	117.19±11.43	101.27±9.23	< 0.001**
Diastolic blood pressure	78.25±8.945	71.30±7.472	< 0.001**

Data were expressed as mean±SD
***P*<0.001 =highly significant

Table 2: Biochemical parameters of the study groups.

Parameter	Gr A BMI≥ 25 n=48	Gr B BMI<25 n=37	p-value
	Mean±SD	Mean±SD	
Bisphenol A (ng/ml)	1.7± 1.0	1.5±0.4	>0.05
Adipokine hormones	9.2±5.66	13.6±7.4	< 0.001**
Adiponectin			
Leptin	30.8±22.2	19.5±15.5	< 0.001**
Lipid profile	182.7±34.2	155.8±23.08	< 0.001**
Total Cholesterol (mg/dl)			
Triglyceride (TG) (mg/dl)	132.86±34.8	112.88±24.7	<0.05*
HDL- Cholesterol (mg/dl)	44.38±5.58	57.03±26.4	<0.05*
LDL - Cholesterol (mg/dl)	115.22±29.61	89.4±29.5	< 0.001**

Data were expressed as mean±SD
***P*<0.001 =highly significant, **P*<0.05 = significant

Table 3: Correlation coefficient between BMI, and the age, waist circumference, BPA, adipokine hormones, lipid profile, and the blood pressure in the studied groups.

Parameter	Body Mass Index (BMI)	
	r	p-value
Waist circumference cm (WC)	0.890	<0.001**
Bisphenol A (ng/ml)	0.2	<0.05*
Adiponectin (µg/ml)	-0.3	<0.001**
Leptin (ng/ml)	0.223	<0.05*
Triglycerides (mg/dl)	0.28	<0.001**
Cholesterol (mg/dl)	0.38	<0.001**
HDL-Cholesterol (mg/dl)	-0.2	<0.05*
LDL-Cholesterol (mg/dl)	0.3	<0.001**
Blood Pressure		
Systolic blood pressure	0.657	<0.001**
Diastolic blood pressure	0.433	<0.001**

** Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

habits with BMI < 25 were used as referent group (Gr B). All subjects who had clinical history of past or present diseases causing dyslipidemia, increasing blood pressure, kidney or liver diseases, and diabetic history as well as those who reported regular drug consumption were excluded from this work. The study protocol was first approved by the Ethical Committee of National Research Centre, and that taken the number (13177). and all participants gave their consents to participate in this work. All participants were interviewed and subjected to a detailed questionnaire including detailed past and present medical and occupational histories. A clinical examination was done for each one. The weight (Wt), height (Ht) and waist circumference (WC) were measured and body mass index (BMI) was calculated according to WHO[27]. Blood pressure was measured for each individual. Whole blood was centrifuged at 12000 rpm for 10 minutes using (Heraeus Labofuge 400R) centrifuge to separate serum and stored at -80^{0}c until analysis.

Biochemical analyses:

Estimation of serum Bisphenol A levels

Serum samples were analyzed for levels of BPA using Glory Science for Human Bisphenol A (BPA) ELISA kit according to manufactory's instruction

Estimation of Adiponectin, and leptin

The concentration of serum adiponectin and leptin protein was determined using (ASSAYPRO for human adiponectin and leptin ELISA kit) according to operation manual.

lipid profile

Serum Cholesterol were estimated using enzymatic colorimetric method by human diagnostic kit according to[28], Triglycerides were determined using Kit from Centronic, Germany, according to[29], High Density

Table 4: Distribution of BMI, WC, blood pressure, and the studied biochemical parameters according to BPA level in the study subjects.

Parameter	Gr I (S.BPA≥ 1.9 ng/ml) n=25 mean±SD	Gr II (S.BPA<1.9 ng/ml) n= 60 mean±SD	p-value
BMI (kg/m2)	32.90± 7.56	26.97± 6.7	<0.001**
Waist circumference WC (cm)	93.80± 15.67	83.39± 14.7	<0.001**
Adipokine hormones Adiponectin	8.8±4.9	12.1± 7.3	<0.05*
Leptin (ng/ml)	25.3±18.6	25.5±20.9	>0.05
Lipid profile			
Triglyceride (TG) (mg/dl)	132±31.2	120.6±32.6	>0.05
Total Cholesterol (mg/dl)	182.1±31.8	166.3± 32.3	<0.05*
HDL Cholesterol (mg/dl)	50.7± 25.4	49.6±15.6	>0.05
LDL Cholesterol (mg/dl)	111± 35.4	100 .8±30.6	>0.05
Blood Pressure			
Systolic blood pressure	114.5±14.28	108.5± 12.32	>0.05
Diastolic blood pressure	77 ±10.3	74.48± 8.355	>0.05

Data were expressed as mean±SD
**P<0.001 =highly significant
*P<0.05 = significant

Lipoprotein Cholesterol were estimated using enzymatic colorimetric method by human diagnostic kit according to[30], and Serum low density lipoprotein cholesterol (LDL-C was calculated using the Friedwald's formula.)

Statistical Analysis

Data were collected and analyzed using the statistical package for social science (SPSS) program version 16.0. Quantitative data were done using the Student's t test and ANOVA. The level of significance < 0.05 was used for significant data and that of < 0.001 for highly significant.

RESULTS

As seen in table (1), there was no statistically significant difference between group A and B concerning their age. The mean levels of Wt, BMI, WC, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in GrA. It is quite apparent from table (2) that the mean levels of leptin, total cholesterol and LDL-C were significantly higher in Gr A, while that of BPA was insignificantly higher in that group. The mean levels of adiponectin and HDL-C were significantly lower in Gr A than Gr B. mThere was a significant positive correlation between BMI and both of BPA and leptin levels ($p< 0.05$). A highly significant positive correlation was found between BMI and waist circumference (W.C), cholesterol, LDL-cholesterol and triglycerides ($p<0.001$). A significant negative correlation was found between BMI and both of adiponectin ($p<0.001$) and HDL-cholesterol ($p< 0.05$) (table 3). The studied population was divided according to their serum BPA concentrations to two groups. Gr I with serum BPA concentration ≥1.9 ng/ml and Gr II whose serum BPA concentration< 1.9 ng/ml. The mean levels of BMI, WC, systolic and diastolic blood pressure were higher in Gr I, compared to Gr II. The difference was statistically significant only for BMI and WC. On the other side the mean levels of cholesterol, triglycerides and LDL-cholesterol were higher in Gr I compared to Gr II. The difference was statistically significant only for cholesterol, Also the mean level of adiponectin was significantly lower in Gr I than that of Gr II ($p< 0.05$) (table4). The study population was classified into four groups, according to their serum BPA concentration. Group 1 (Gr 1) was having the lowest concentration of BPA < 1 ng/ml, while group 4(Gr 4) included those with highest serum BPA concentration > 1.8 ng/ml. The mean levels of BMI were increasing with increasing serum concentration of BPA with the exception of 3rd group. Concerning the key of adipokine hormones, adiponectin level showed a significant nonlinear relation-ship across the groups. As regards the mean levels of the total cholestrol (TC) and the LDL-C both of them showed crescendos decrease across the first three groups. Then they increased in group 4 (Gr 4) with the highest concentration serum BPA. The mean level of systolic blood pressure showed an increase across the groups, while it decreased in the 3 rd group, and their differences were statistically significant (p <0.05) as seen in table (5).

DISCUSSION

The results of the present study revealed the presence of Bisphenol A in the serum of all participants, which is going with many studies[31-33]. As, they reported that BPA could be detected in the blood and urine of most people worldwide indicating its ubiquitous exposure. In humans, body mass index (BMI) and obesity are two of the most studied endpoints in regard to BPA exposure. The reviews of[34] and that of[35] on BPA exposure and obesity in human populations conflicting. Some studies observed a statistically significant positive correlation between urinary or serum BPA levels and BMI, and others observed no correlation or association. Trasande *et al.*(2012)[36] reported the possibility of individuals with increased BMI have higher caloric intake and may be exposed to higher concentrations of BPA through food packaging or other lifestyle factors. In this study, the mean level of BPA in Gr A (1. 7 ± 1.0 ng/ml) was higher than that of Gr B (1.5±0.4

Table 5: Distribution of the mean levels of the measured anthropometric parameters, adipokine hormones, lipid profile, and blood pressure, according to serum BPA concentration the studied groups.

Variables	(Gr 1) BPA<1ng/ml n=23 Mean ±S. D	(Gr 2) BPA> 1-1.3ng/ml n=11 Mean ±S. D	(Gr 3) BPA <1.3-1.8 ng/ml n=26 Mean ±S. D	(Gr 4) BPA>1.8 ng/ml n=25 Mean ±S. D	P value
Age (years)	33.48±12.67	34.55±9.97	35.46±10.83	37.32±9.56	> 0.05
Weight (kg)	74.62±15.9	82.75±30	63.44±10.753	84.64±19.91	<0.001**
Height (cm)	162.30±5.26	160.73±5.27	162.50±4.84	160.37±4.14	> 0.05
BMI (kg/m2)	28.15±5.10	31.74±11	23.91±3.86	32.90±7.56	<0.001**
WC (cm)	86.09±13.00	91.36±24.4	77.63±7.68	93.80±15.67	<0.001**
Adipokine hormones Adiponectin	12.66±8.11	7.25±4.47	13.49±6.98	8.89±4.95	< 0.05*
Leptin	26.38±23.87	27.84±26.02	23.39±15.80	25.32±18.65	>0.05
Lipid profile Triglyceride (TG) (mg/dl)	124.47±44.475	121.73±20.79	116.65±23.813	131.96±31.16	>0.05
Total Cholesterol (mg/dl)	174.30±39.91	172.55±32.24	157.23±22.11	182.16±31.83	< 0.05*
HDL Cholesterol (mg/dl)	45.96±7.048	45.27±3.636	54.73±21.837	50.68±25.437	>0.05
LDL Cholesterol (mg/dl)	113.78±32.33	106±32.70	88.12±22.41	111.12±35.42	< 0.05*
Blood Pressure Systolic blood pressure	110.87±12.4	114.55±14.3	103.81±9.81	114.52±14.28	< 0.05*
Diastolic blood pressure	75.35±9.60	77.09±9.00	72.62±6.61	77.00±10.30	>0.05

Data were expressed as mean±SD
***P*<0.001 =highly significant
**P*<0.05 = significant

ng/ml), but the difference was statistically insignificant (p>0.05) (table 2), and there is a significant positive correlation between BPA levels and BMI in the participated women (r= 0.2, p<0.05) (table 3). This is consistent with Takeuchi *et al.*(2004)[9], who found that the obese group had higher serum BPA concentrations than the non-obese group. They also concluded that there was an association between increased serum BPA levels and increased BMI in women. Also, our results are in accordance with those reported by[10] and[37], who found that increased urinary BPA was significantly correlated with increased BMI and WC. They also insured that BPA was correlated with both general and central obesity in adults. Furthermore, Zhao *et al.*(2012)[38] detected that urinary BPA was positively correlated with body weight, BMI, fat mass even in non-obese persons. However, some studies[39,40] could not detect any relationship between BPA and obesity indices. They explained their results by considering obesity as a multifactorial disease and weight gain often occurs at a slow rate, which makes it difficult to establish a relationship between BPA level in serum measured at one time point and fat volume accumulated over years. diponectin is a hormone secreted exclusively by adipocytes that regulates the metabolism of lipids and glucose[41]**.** So, it protects against metabolic syndrome[42], which is characterized by the presence of abdominal obesity, hypertriglyceremia and hypertension, glucose intolerance, hyperinsulinemia, and is associated with increased risk of diabetes and cardiovascular disease[43]. In this work, we found that adiponectin mean level is significantly lower in Gr A (9.2 ± 5.6) than that of Gr B (13.6 ± 7.4) (table 2) and adiponectin levels showed significant negative correlation with BMI (table 3). Our results are in accordance with[44,45], who concluded that, although, adiponectin secreted from adipose tissue, is inversely related to fat mass and it was found to be decreased in obese**.** Also, our findings are consistent with those of Cohen *et al*., (2011)[61] who found that adiponectin was lower among overweight and obese women compared to non-obesewomen, and there was a monotonic reduction in adiponectin over increasing BMI[46]. Moreover, Kadowaki, Yamauchi[47] found that adiponectin levels are inversely associated with obesity and are found to be decreased in individuals with increased adiposity through down-regulation of adiponectin receptors[47]. This inverse relation has been confirmed via our study (table 3), as

adiponectin levels were significantly negatively correlated with the BMI of the studied female participants (r=-0.3, p<0.003). In contrast[48], found no significant correlation between serum adiponectin and BMI. Leptin, is a lipostatic hormone that contributes to body weight regulation through modulating feeding behavior and energy expenditure[49,50]. Plasma leptin levels correlate positively with adiposity, however, obese individuals commonly develop 'leptin resistance' or tolerance causing a hyperleptinemic state with a lack of leptin's regulatory effects[51,52]. Serum leptin concentration was shown to be increased in humans with obesity, insulin resistance and dyslipidemia[53,54]. The increased serum leptin concentration in obesity was proposed to be secondary to 'leptin resistance' which is described as a reduced sensitivity with respect to the anorectic response to exogenously administrated leptin[55]. The mechanisms of leptin resistance still remain unclear, but at least 3possibilities have been postulated to carry it: (a) an inability of circulating leptin to reach its targets in the brain; (b) reduction of LEPR expression; and/or (c) an inhibition of the signaling events within selected neurons in specific brain regions[56-59]. Furthermore, Lee, Reed, Price[60] demonstrated that leptin resistance is strongly associated with extreme obesity and appears to be a heritable trait. In our study, the leptin level was significantly higher in group A (30.8 ± 22.2) than group B (19.5 ± 15.5) (table 2). Also, its levels correlate positively with increased BMI (r= 0.2, p<0.04) (table 2). Same results were found by many authors[46,48,61]. They found that leptin increased with increasing BMI and significantly correlates with it. The same was even found in children by[62], who found that children with higher BMI had higher levels of leptin and this made them eligible to develop adult obesity. The incidence of obesity and its related disorders as dyslipidemia, and hypertension have been constantly increased, and also have been associated with adult BPA exposure. In the present study, we observed dyslipidemia in Gr A represented by significant higher triglycerides, total cholesterol, LDL-C and lower HDL-C in Gr A than those of Gr B (table 2). In addition, the triglycerides, cholesterol, LDL showed positive significant correlation with increasing BMI of the study groups, while HDL showed a significant negative one. It was also detected that obese group was having higher significant value of both systolic and diastolic blood pressure compared to the non-obese (table 2). Our results could be related to the decrease of adiponectin levels in obese individuals, which is responsible for regulation of lipid and glucose[41,42]. The dyslipedimic changes and hypertension associated with obesity have been discussed by[63,46]**.** The former confirmed that adiponectin and leptin DNA methylation correlates with obesity and the lipid profile. The adiponectin and leptin hormone levels was found to respond faster to changes of BPA[40], they found that BPA is related strongly with adiponectin and leptin, but not to fat mass or fat distribution in humans, suggesting that BPA may interfere with hormonal control of hunger and satiety. In our work, when the study subjects were divided into two groups according to serum bisphenol A concentrations, we observed a significant lower adiponectin level in the high BPA Gr. than that of the low BPA Gr. Our findings are strongly evidenced by[12], who found that even low doses of BPA exposure that are similar to environmental dose at (0.1 &1 nM) inhibits adiponectin release that protects from the sequelae of the metabolic syndrome in humans. They also concluded that BPA at environmental concentrations suppressed adiponectin release from human adipose tissue explants as well as from isolated mature adipocytes. Moreover, the suppressive effect of BPA on adiponectin level was as effective, and often more effective, than equimolar concentrations of 17 β- estradiol (E2). Meanwhile, we observed that non- significant difference in between the two groups, concerning their mean leptin level, and this in accordance with[64]. The high bisphenol group was having a dyslipidemic changes in the form of higherlevels of serum cholesterol, LDL, TGs in compared to the low one, which explains the higher blood pressure observed in Gr. A individuals. The difference was statistically significant only for serum cholesterol. Similar results were obtained by[31]. They found that higher total serum BPA was associated with higher levels of low density lipoprotein (LDL-C), and cholesterol levels. Additionally, BPA often exhibits a lack of linear dose-dependent relationship, showing instead U-shaped or inverted U-shaped curves. Consequently, lack of action, of BPA at high doses to its presumed bioactivity at low doses is unwarranted. As well as, BPA has been used as one of the most frequent models for demonstrating the low dose and non-monotonic nature of hormones that regulate or affect the endocrine system[65,66]. Non-monotonic dose–response curves (NMDRCs) indicate a change in the direction (i.e. sign) of a dose–response curve slope. These could be seen clearly in table 5, in which the anthropometric measures followed this pattern and the differences between groups were found significant. The adipokine hormones showed the same pattern, however the variability in adiponectin levels were the only one which showed significance. The lipid profile showed the NMDRCs pattern and the cholesterol and the LDL-C were the two parameters that showed significance. The systolic and diastolic blood pressure followed the Z- shaped pattern and the significance was only for the systolic blood pressure across the groups.

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