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INSULIN RESISTANCE AMONG BISPHENOL A EXPOSED WORKERS IN FIBERGLASS PIPES INDUSTRY

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Abstract:

Introduction: Despite that bisphenol A (BPA) was widely used in industry, it can exert a number of toxicological effects on tissues mainly the endocrine system through its estrogenic action. **Aim of work:** The aim of the study was to evaluate the possible effect of occupational exposure of BPA on insulin homeostasis and diabetes mellitus. **Materials and Methods:** A case control cross sectional study was performed in one of the international factories manufacturing fiberglass and PVC pipes located in 6th of October City. The study population was divided into 2 groups; an exposed group consisted of 40 workers occupationally-exposed to BPA and a control group of 45 workers from outpatient clinic in Kasr Al Aini hospital. The exposed group was subdivided into 2 subgroups according to insulin resistance index: 1) Bisphenol A exposed subgroup with insulin resistance index < 4 (n=31), 2) Bisphenol A exposed subgroup with insulin resistance index ≥ 4 (n=9). The whole studied population was subjected to a detailed questionnaire including personal and medical history. General and systemic examinations were performed in addition to measuring both height and weight to all subjects to calculate BMI. All participants were subjected to laboratory investigations in the form of serum insulin level, fasting blood sugar (FBS) and 2 hours post prandial blood sugar level (2hPPBS). Urine level of BPA was estimated as a biomarker for BPA exposure. Statistical analysis was done using (SPSS) Statistical Package for Special Sciences version 16. **Results:** This study showed an elevation in urinary BPA level among workers as well as an increased insulin level, fasting blood sugar and post prandial blood sugar levels. The prevalence of type 2 diabetes mellitus and insulin resistance was higher among the exposed group with positive correlation with the urinary BPA level. Conclusion: occupational exposure to BPA increases the risk of developing insulin resistance and type 2 diabetes mellitus.

Key words: Bisphenol A, Xenoestrogen, Insulin, Insulin resistance and Diabetes Mellitus.

Introduction

Environmental chemicals with estrogenic activities "xenoestrogens" (XEs) are natural or industrial compounds that are capable of mimicking the effect of the endogenous estrogen or interfere with estrogen signaling pathways through binding to estrogen receptors. Thus, XEs can cause alteration of endogenous hormones at the level of their synthesis, storage, metabolism, transport, elimination and binding to their specific receptors (Kerdivel et al., 2013).

Bisphenol A (BPA) is one of these estrogenic xenobiotics which was first synthesized in 1891. Later in the 1930s, it was investigated during the search for synthetic estrogens and was tested for its estrogenic properties (Vandenberg et al., 2009). Nowadays, BPA is one of the highest volume chemicals produced worldwide, with more than 10 billion pounds per year in 2011 and over 100 tons released into the atmosphere by yearly production (vom Saal et al., 2012). It is widely used in industry as a monomer for the synthesis of polycarbonate plastics, epoxy resins, vinyl and unsaturated polyester resins. It is also used as an antioxidant in polyvinyl chloride (PVC) plastics and as an inhibitor of end polymerization. Epoxy resins containing BPA are used as protective lining for food and beverage cans (Gharravi et al., 2005) and as coatings for PVC pipes to give pipes a good corrosion resistance, smooth interior wall and good thermal insulation (Xu et al., 2009).

Human exposure to BPA may occur during environmental scenarios due to migration of BPA from food contact material into food. However, occupational exposure may occur due to inhalation of BPA dust particles and through dermal route (Ormond et al., 2009). The European Food Safety Authority (EFSA) adjusted the tolerable daily intake of BPA for The European Union at 0.05 mg/kg/day (EFSA, 2008).

BPA exerts its action through binding to estrogen receptors (Vandenberg et al., 2009). Studies suggest that BPA can interfere with normal development of the neurologic and reproductive systems and damage hepatocytes. Also, BPA exposure is associated with increased risk of cancer, heart disease and sexual dysfunction. More recent studies have documented that the estrogenic effect of BPA can disrupt the pancreatic ß- cell function and induce insulin resistance and type 2 diabetes mellitus (Gong et al., 2013).

Insulin resistance is defined as an insensitivity of the peripheral tissues (e.g., muscle, liver, adipose tissue) to the effects

of insulin. This leads to impaired ability of plasma insulin to promote peripheral glucose disposal and suppress hepatic glucose uptake (Caceres et al., 2008). To maintain glucose homeostasis, a compensatory increase in insulin secretion occurs and normoglycemia is maintained leading to a state of chronic hyperinsulinemia. Failure of this compensatory response leads to diabetes (Tfayli and Arslanian, 2009).

Aim of work

The aim of the study was to evaluate the possible effect of occupational exposure of BPA on insulin homeostasis and diabetes mellitus.

Materials and Methods

A case control cross sectional study that was performed in one of the international factories manufacturing fiberglass and PVC pipes located in 6th of October City. The factory produces different types of reinforced pipes in addition to different types of fittings and joints.

The study population was divided into 2 groups; an exposed group consisted of 40 workers occupationally-exposed to BPA. The factory comprised 550 workers (150 workers in the shift at time of sampling). After applying inclusion criteria (continuous work duration of more than 5 years and working in area of the production line) and excluding of workers whose work duration is less than 5 years and those known to be diabetics before onset of work, about 105 workers were accepted to participate in the study. Seventeen workers were excluded because they refused to share in the study. The rest of workers, total of 88 workers, were listed on the computer and randomly selected 40 subjects.

As for the control group 45 male subjects were selected from the industrial medicine and occupational diseases outpatient clinic in Kasr Al Aini hospital as they had never been occupationally exposed to BPA. They were matching with the exposed workers in age, sex, socioeconomic status, dietary habits and special habits of medical importance.

The exposed group was subdivided into 2 subgroups according to insulin resistance index : 1) Bisphenol A exposed subgroup with insulin resistance index < 4 (n=31). And 2) Bisphenol A exposed subgroup with insulin resistance index ≥ 4 (n=9).

The work place in all departments was suitable for workers as regards ventilation, illumination and water supply and most of the workers were wearing personal protective equipments including gloves, helmets, boots and eye googles. A written consent to share in the study and an approval to give blood samples and to be

clinically examined from each individual were obtained after explaining the aim and importance of the study.

The whole studied population was subjected to a detailed questionnaire including personal and medical history. Also, detailed occupational history including duration of employment, department, description of the current job and previous jobs, if present, either in the same place or in other places, the use of protective equipment and state of ventilation in the workplace were conducted for all subjects. General and systemic examinations were performed in addition to measuring both height and weight to all subjects to calculate BMI.

All participants were subjected to laboratory investigations in the form of serum insulin level, fasting blood sugar (FBS) and 2 hours post prandial blood sugar level (2hPPBS). Urine level of BPA was estimated as a biomarker for BPA exposure.

Assessment of urinary BPA level (conjugated and free) was done by using HPLC (High-performance liquid chromatography) (Ouchi and Watanabe, 2002). Assessment of serum insulin level was measured by monoclonal antibody based sandwich enzyme-linked immuno sorbent assay (ELISA) (Røder et al., 2009). Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR). It was calculated through this equation:

HOMA -IR = (FPI FPG) / 22.5

FPI: fasting plasma insulin concentration (mU/l)

FPG is fasting plasma glucose (mmol/l) (Keskin et al., 2005).

The scores ≥ 4 indicated the existence of insulin resistance with higher levels representing greater degrees of insulin resistance and scores < 4 as insulin sensitive (Reinher and Andler, 2004).

Calculation of body mass index (BMI): Body mass index was calculated according to the following formula:

BMI = weight (kg) / height (m^2) kg/m^2 (Wang et al., 2012)

Statistical analysis

The data were processed and analyzed using the program (SPSS) Statistical Package for Special Sciences version 16. Data were compared using Chi Square ($\chi 2$) test for qualitative variables and the independent simple t-test as well as the analysis of variance (ANOVA test) followed by Post Hoc test for normally distributed quantitative variable. The non-parametrical Mann-Whitney and Kruskal-Wallis tests

were used for quantitative variables not normally distributed. Correlations were done to test for the presence of linear relations between quantitative variables. The statistical significance was defined as $P < 0.05$.

Results

The study population consisted of 85 male subjects. The exposed group consisted of 40 workers, whose ages ranged from 27-59 years old with mean of 35.23 ± 5.8 years showing no statistical significant difference when compared with the control group (range=26-54 years, mean=37.60 ± 8.48 years). As for the exposed group, work duration ranged from 5- 27 years with a mean of 8.78 ± 3.86 years. The mean BMI of the exposed group was 28.13 ± 4.20 with no statistical difference of significance when compared with that of the control subjects (mean= 25.80 ± 1.49).

According to the medical history, the percentage of workers having a family history of DM among the exposed workers was 25% (n=10) with no statistical significant difference when compared with that of the control subjects (20%) (n=9). Also, only 2 cases (5%) were known to have DM prior to our investigations in the exposed group while there were 3 cases (6.7%) known to be diabetics in the control group with no statistical difference ($p>0.05$).

Table 1: Mean± SD of BPA level in urine (ng/ml), serum insulin (μU/ml), insulin resistance index, FBS (mg/dl) and PPBS (mg/dl) in both BPA exposed group (n=40) and control group (n=45):

	Exposed group (n= 40)	Control group (n= 45)	P value
Bisphenol A level in urine (ng/ml)	4.76 ± 5.47	0.14 ± 0.09	0.001**
Serum insulin (μU/ml)	13.27 ± 2.94	10.94 ± 1.29	0.001**
Insulin resistance index	3.22 ± 1.15	1.93 ± 0.42	0.001**
FBS (mg/dl)	98.75 ± 26.08	71.20 ± 10.96	0.001**
PPBS (mg/dl)	201.33 ± 47.94	147.64 ± 18.34	0.001**

**p<0.001= highly significant.

Table 1 showed a significant statistical differences between the exposed and control groups as regards BPA in urine, serum insulin, insulin resistance index, FBS and PPBS ($p<0.001$).

Table 2: Frequency distribution of positive cases of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes among BPA exposed group (n=40) and control group (n=45):

	Exposed group (n= 40)	Control group (n= 45)	P value
IFG (FBS 100-125 mg/dl)	12 (30%)	2 (4.4%)	<0.05*
IGT (PPBS 140-199 mg/dl)	20 (50%)	7 (15.6%)	<0.05*
Diabetics			
FBS ≥126 mg/dl	7 (17.5%)	0	<0.05*
± PPBS ≥200 mg/dl	12 (30%)	7 (15.6%)	<0.05*

Data were expressed as number (%).

*p< 0.05= significant.

Table 2 showed that the prevalence of positive cases of IFG, IGT and diabetes was found to be significantly higher (p< 0.05) among the exposed group when compared to the control .

Table 3: Mean ± SD of age, BMI and work duration in BPA exposed subgroup [insulin resistance index < 4 (n= 31)] and BPA exposed subgroup [insulin resistance index ≥4 (n= 9)].

	Insulin resistance level		P value
	< 4 (n= 31)	≥ 4 (n= 9)	
Age (year)	34.42 ± 4.30	38.00 ± 9.30	>0.05
BMI	28.06 ± 3.84	28.33 ± 5.55	>0.05
Work duration (year)	8.23 ± 2.25	10.67 ± 6.96	>0.05

NS= p> 0.05= not significant.

The exposed group was further divided according to insulin resistance index and there was no significant statistical difference in the mean age, BMI and work duration between the two subgroups.

Table 4: Mean± SD of BPA level in urine (ng/ml), serum insulin (μU/ml), insulin resistance index, FBS (mg/dl), PPBS (mg/dl) in BPA exposed subgroup [insulin resistance index < 4 (n= 31)] and BPA exposed subgroup [insulin resistance index ≥ 4 (n= 9)]:

	Insulin resistance level		P value
	< 4 (n= 31)	**≥ 4 (n= 9)**	
BPA level in urine (ng/ml)	3.09 ± 3.50	10.51 ± 7.23	0.001**
Serum insulin(μU/ml)	12.53 ± 2.73	15.79 ± 2.25	0.001**
FBS (mg/dl)	90.70 ± 21.36	126.50 ± 22.08	0.001**
PPBS (mg/dl)	190.11 ± 39.35	239.96 ± 56.84	0.001**

**p< 0.01= highly significant.

Table 4 showed that there was a highly statistical significant difference between exposed subgroup with insulin resistance index ≥4 and exposed subgroup with insulin resistance index <4 (p<0.001).

Table 5: Correlation between BPA level in urine with different laboratory parameters including serum insulin (μU/ml), insulin resistance index, FBS (mg/dl), PPBS (mg/dl) in BPA exposed group:

	r	P value
Insulin level (μU/ml)	0.205	>0.05
Insulin resistance index	0.489	<0.05*
FBS (mg/dl)	0.499	<0.05*
PPBS (mg/dl)	0.493	<0.05*

r= correlation coefficient.

NS= p> 0.05= Not significant.

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

Table 5 revealed statistically significant positive correlation between BPA level in urine and insulin resistance index, FBS and PPBS (p< 0.05). However, no significant correlation was found between BPA level in urine and insulin level (p>0.05).

Moreover, data revealed no significant correlation between BPA level in urine and different exposure parameters including age, work duration and BMI (p>0.05).

Discussion

In the current study, the mean concentration of BPA in exposed workers was remarkably higher than that of their matched referents (4.76 ± 5.47 versus 0.14 ± 0.09, P< 0.05) (Table 1). This is in accordance with the results reported by Hanaoka et al., (2002) who found that mean urinary levels of BPA in epoxy resin sprayers was about double that of unexposed workers and they concluded that estimation of urinary BPA was suggested as a possible biological monitoring method for BPA exposure. Also, Hee et al., (2009) on his study on Chinese workers exposed to BPA and epoxy resins revealed that over 90% of exposed workers have notable levels of BPA in their serum and urine.

Our study showed that the age, duration of work and BMI had no effect on the level of urinary BPA. This is in accordance with Calafat et al., (2005) who studied age-related changes in the urinary excretion of BPA and mentioned that urinary excretion of BPA does not show any significant age-related variations. Moreover, Mahalingaiah et al., (2008) could not find strong relationships of urinary BPA concentrations with age, sex and BMI.

Our work showed that duration of work is not correlated with urinary BPA level and this can be explained by that BPA is metabolized in humans via hepatic glucuronidation and sulfation. The major metabolite is BPA-G (water soluble) is rapidly excreted through kidneys with half-life of approximately 6 hrs and complete urinary excretion in 24 hr (Volkel et al. 2002). However, BPA has long term adverse health effects because the fact that being lipid soluble, a fraction of the absorbed BPA distributes to body storage sites followed by a slow release into the bloodstream and urine resulting in a low-dose continuous exposure (Fernandez et al., 2007). Moreover, β-glucuronidase enzyme, present in placenta and intestine, is able to deconjugate BPA and thus release its active form again (Genuis et al., 2012).

In the current work, comparison between the exposed and control group regarding both serum FBS and serum PPBS revealed statistically significant increase in their levels in exposed group rather than the controls (Table 1). Also, findings revealed significant correlation between urinary BPA level and both serum FBS and serum PPBS ($p< 0.05$) (Table 5). This comes in harmony with Wei et al., (2011) who observed that prenatal BPA exposure in rats resulted in increased body weight, FBS and impaired glucose tolerance in adult offspring. Shankar and Teppala, (2011) as well, concluded that urinary BPA levels are found to be associated with DM.

In spite of the elevated serum glucose level, our results show an elevation of insulin level with significant statistical difference between exposed and control groups (Table 1). In addition, positive correlation was detected between serum insulin and urinary BPA but with no statistically significant difference (Table 5). This goes in accordance with Batista et al., (2012) who reported that short exposure of adult mice to BPA induces insulin resistance and a strong tendency to hyperinsulinaemia in the fed state, together with decreased glucose levels.

Hyperinsulinaemia caused by BPA exposure can be explained by many theories. One theory is the effect of BPA on glucagon secretion through both of cAMP and [Ca+2] osscillation. Glucagon release is stimulated by absence of glucose and is maximally inhibited when the sugar concentration approaches the threshold for stimulation of insulin secretion (Tian et al., 2011). In fact, BPA completely suppressed [Ca+2] oscillations in pancreatic cells and decreasing glucagon secretion (Alonso-Magdalena et al., 2005). In addition, BPA increased β-cell insulin content and release as well as changes in insulin gene expression (Lin et al., 2013). Another explanation of hyperinsulinemia is the direct effect of BPA on peripheral tissue reducing the overall energy metabolism and leads to insulin resistance in liver and skeletal muscle together with β-cell exhaustion (Soriano et al., 2012). Moreover, BPA suppress adiponectin release (a hormone secreted exclusively by adipocytes that regulates the metabolism of lipids and glucose) from human adipose (Hugo et al., 2008). Adiponectin increases fatty acid oxidation and glucose metabolism in muscle, and reduces glucose output and enhances insulin sensitivity in liver. Many studies provide that BPA suppresses adiponectin through inhibition of protein disulfide isomerase enzyme which is responsible for formation of disulfide bonds of adiponectin molecules (Ben-Jonathan and Hugo, 2009).

In the present study, there was no significant difference in the mean age, BMI and work duration between the two subgroups ($p>0.05$) (Table 3). This could be explained by the fact that impact of age on insulin resistance is focused on time of puberty which is associated with transient increases in insulin resistance and complete recovery by pubertal completion and this is accepted as a normal physiologic condition (Kurtoğlu et al., 2010). Furthermore, the age of the exposed group in our study ranged from 27-59 years old with mean of 35.23 ± 5.8 which is far away from that critical age of puberty. In their study, Lee et al.,

(2006) observed that among normal weight and overweight adolescents, homeostasis model assessment for insulin resistance (HOMA–IR) values did not differ substantially between ages; however, there was an apparent peak at age 14 years among obese adolescents. Moreover, Kurtoğlu et al., (2010) found no difference in BMI values between groups with and without insulin resistance, except for pubertal girls. This finding indicates that BMI values are not always correlated with body fat ratio.

It is known that BMI is a surrogate measure of adiposity which correlates with fat-free mass and total body fat. Most of the cohort studies demonstrated that waist circumference is believed to be a more precise predictor of insulin resistance (IR) in children and adults (Kotlyarevska et al., 2011) because of the fact that abdominal fat is more lipolytically active than subcutaneous fat and yet more resistant to the antilipolytic effects of insulin. Since the output of visceral fat drains into the hepatic portal blood, an increased influx of free fatty acids leads to inhibition of insulin clearance by the liver, thus contributing to hyperinsulinemia (Ben-Jonathan and Hugo, 2009).

Conclusion

Our results revealed that the workers exposed to BPA in the fiberglass pipes industry have increased level of urinary BPA compared to control group. Also, the increased BPA is associated with high prevalence of insulin resistance and type 2 DM among workers. Therefore, environmental monitoring of BPA in the workplace is important and it is suggested to use BPA in urine as a biomarker for BPA exposure. Also, pre-employment and periodic examinations of the workers beside the use of protective equipments are recommended.

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