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RESEARCH ARTICLE

Metabolic and endocrine effects of bisphenol A exposure in market seller women with polycystic ovary syndrome

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Abstract Bisphenol A (BPA) is one of the synthetic monomer which can be found in the environment. Limited animal and human studies have demonstrated that BPA alters endocrine and or metabolic functions. The aims of the present study were to evaluate serum BPA level in marketing seller women with polycystic ovary syndrome (PCOS) and hormonal and metabolic effects of this exposure compared to a control paired group. In a case-control study, 62 PCOS women who work as marketing sellers and 62 healthy women with similar jobs were included. The two groups were body mass index (BMI)- and age-matched. Serum samples were analyzed for BPA content, fasting blood sugar (FBS), triglyceride, cholesterol, HDL and LDL levels, thyroid stimulating hormone (TSH) concentration, and LH:FSH ratio. Significant higher serum BPA content (0.48 ± 0.08 vs. 0.16 ± 0.04 ng/ml), triglyceride (103.05 ± 13.10 vs. 91.65 ± 12.52 mg/dl), cholesterol (165.05 ± 10.79 vs. 161.21 ± 10.31 mg/dl) levels and LH:FSH ratio (3.64 ± 0.86 vs. 0.62 ± 0.14) and significant lower TSH concentration (1.56 ± 0.68 vs. 2.15 ± 1.09 IU/ml) were detected in case against control group, respectively ($P < 0.05$). No significant differences were detected in FBS, LDL, and HDL levels between the two groups. Also, there were no significant associations between serum TSH concentration and BPA level neither in case ($P = 0.269$) nor in control ($P = 0.532$) groups. In BPA-exposed PCOS women, BPA level was higher than healthy women and this difference maybe the cause of significant differences in levels of triglyceride, cholesterol, TSH, and LH:FSH ratio. These observations confirm the potential role of BPA in PCOS pathophysiology.

Keywords Bisphenol A · Polycystic ovary syndrome · Sellers · Lipid profile · Thyroid stimulating hormone

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of 6–10 % of young women with the main features of hyperandrogenism, insulin resistance, and chronic anovulation (Diamanti-Kandarakis et al. 1999; Majumdar and Singh 2009). This syndrome can cause complications in appearance and induces reproductive disorders (Vural et al. 2005). The clinical signs of patients include irregular menstrual cycle, increased androgens, body mass index (BMI), hirsutism, and severe acne. Also, metabolic disorders such as high insulin levels and risk of type II diabetes, cardiovascular diseases, and reproductive disorders such as large double-sided ovary, ovarian volume increase, lack of ovulation, and infertility were reported (Majumdar and Singh 2009). However, the etiology and pathophysiology of PCOS are not yet clearly identified.

Both human and animal studies have suggested the potential role of bisphenol A (BPA) in the pathogenesis of PCOS (Akın et al. 2015; Fernández et al. 2010a). BPA is a high-production volume industrial chemical mainly used as a monomer in the production of polycarbonate plastics and epoxy resins (Halden 2010; Klar et al. 2014). BPA is a commercially important chemical with an estimated worldwide production capacity of 3.7 million metric tons per year (Week 2005). Thermal paper contains BPA in its un-reacted form as an additive that is used in sales receipts (Pivnenko et al. 2015). It was shown that the level of BPA in women with PCOS is significantly higher than in healthy women (Kandaraki et al. 2010). In addition, neonatal rats which were exposed to BPA developed PCOS-like syndrome in adulthood (Fernández et al. 2010a).

Until recently, there were relatively few epidemiological studies examining the relationship between BPA and metabolic/endocrine effects in PCOS especially in seller workers. Thus, the aims of the present study were to evaluate and compare the metabolic profiles and serum BPA in two women groups with and without PCOS who work as market sellers.

Materials and methods

Participants

In this case-control study with assumption of α = 0.05, β = 0.20, case:control ratio = 1, effect size = 0.50, standard deviation of the outcome in the population = 0.99, and the total number of 124 Persian participants from four main hypermarkets in Tehran, the capital of Iran, were enrolled. Sixty-two healthy women who worked in the market without BPA exposure as control group and 62 age- and body mass index (BMI)-matched marketing sellers women with BPA exposure as case group were included. The index of BPA exposure was contact with thermal paper which used in automated teller machine (ATM), point of sale (POS), and other automated seller devices.

Blood sampling and serum assessment

Fasting blood samples were taken from the cubital vein into sterile vacutainers without anticoagulant and after centrifugation (2000*g*, 10 min); the serum was stored at −20 °C until used. The fasting blood sugar (FBS) and serum triglyceride, cholesterol, HDL, and LDL levels were measured using auto-analyzer and reported as milligram per deciliter. Thyroid stimulating hormone (TSH) activity (IU/ml) was measured using ELISA (Abcam, UK). Luteinizing hormone to follicular stimulating hormone (LH:FSH) ratio was calculated for both groups as index of PCOS. The serum BPA level (ng/ml) was assessed by HPLC method.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) analyzed by IBM SPSS software version 23. Two independent sample *t* test was used for between-group comparison, and *P* value lower than 0.05 was considered as significant differences. GraphPad Prism 6 was used to draw the charts.

Results

All participants were BMI- and age-matched and there are no significant differences between the control and case groups neither in BMI (22.47 ± 1.51 kg/m^2 vs. 22.47 ± 1.51 kg/m^2, P = 1.000) nor in age (28.56 ± 3.29 years vs. 29.24 ± 3.11 years, P = 0.241). The BPA concentration in the case group was significantly higher than that in the control group (P < 0.001, Fig. 1).

The effects of exposure to BPA on serum biochemical parameters were shown in Table 1. There were no significant differences in FBS, HDL, and LDL concentrations between the case and control groups (P > 0.05). But significantly higher serum triglyceride and cholesterol concentrations and lower TSH level were detected in the case group against the control group (P < 0.05). Also, no significant associations between serum TSH concentration and BPA level were detected neither in the case group (P = 0.269) nor in the control (P = 0.532) group.

The LH:FSH ratio was shown in Fig. 2. The ratio level in the case group is significantly higher than that in the control group (P < 0.001) which confirms the existence of PCOS in the case group rather than in the control group.

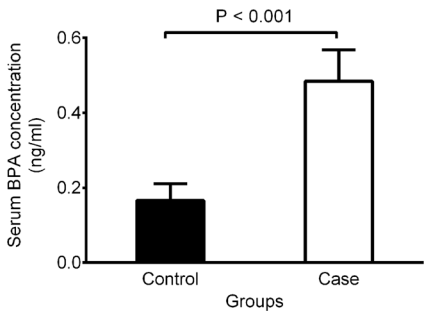

Fig. 1 Serum bisphenol A (BPA) concentration which was assessed by HPLC method in nanogram per milliliter. Sixty-two healthy women who worked in market without BPA exposure as the control group and 62 age- and BMI-matched marketing sellers women with BPA exposure as the case group

Table 1 Comparison of serum biochemical parameters as mean ± SD between the case and control groups (n = 62 for each group)

Parameters*	Groups		P values**
	Control	Case	
FBS (mg/dl)	80.23 ± 5.89	79.95 ± 6.26	0.802
Triglyceride (mg/dl)	91.65 ± 12.52	103.05 ± 13.10	<0.001
Cholesterol (mg/dl)	161.21 ± 10.31	165.05 ± 10.79	0.045
HDL (mg/dl)	49.00 ± 2.71	48.44 ± 2.54	0.234
LDL (mg/dl)	94.18 ± 9.82	96.77 ± 11.08	0.170
TSH (IU/ml)	2.15 ± 1.09	1.56 ± 0.68	0.001

**FBS* fasting blood sugar, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TSH* thyroid stimulating hormone

**This P values are provided by two independent sample t test for between-group comparison

Discussion

In the present study, the effects of exposure to BPA on biochemical and endocrine parameters in seller women who works in marketing with and without exposure to BPA were evaluated. Also, the PCOS probability was checked by the measurement of LH:FSH ratio. We found that the BPA concentration in the case group was significantly higher than that in the control group which caused to significantly increase serum triglyceride and cholesterol concentrations, plus to LH:FSH ratio, and decrease TSH level in the case group against the control group. Other parameters did not show significant differences.

PCOS is the most frequent endocrinopathy in women of reproductive age and it could be seen in both obese and lean women (Diamanti-Kandarakis et al. 1999). It has been reported that women with PCOS show more carbohydrate metabolism disorders, such as impaired glucose tolerance or frank diabetes mellitus, against BMI-matched ones (Kandaraki et al. 2010). The role of BPA contact in PCOS induction is partially confirmed. BPA can interact with estrogen receptors due to its molecular structure which disrupted sexual hormone pathways (Rutkowska and Rachoń 2014). Also, BPA induces modifications of ovarian steroidogenic enzymes and steroidogenic acute regulatory protein which some of them are related to PCOS hyperandrogenism (Nelson et al. 2001; Zhou et al. 2008). In another way, BPA can interrupt neuroendocrine regulation of ovary in animal model (Nikaido et al. 2004). Thus, BPA has the potential ability to deteriorate the reproductive axis and induce PCOS (Palioura and Diamanti-Kandarakis 2015). In point of animal study, Fernandez and colleagues reported that when 10-day-old female rats were exposed to BPA reached adulthood, they exhibited elevated testosterone levels, anovulation, infertility, polycystic ovarian morphology, and increased gonadotropin-releasing hormone (GnRH) pulse frequency (Fernández et al. 2010b).

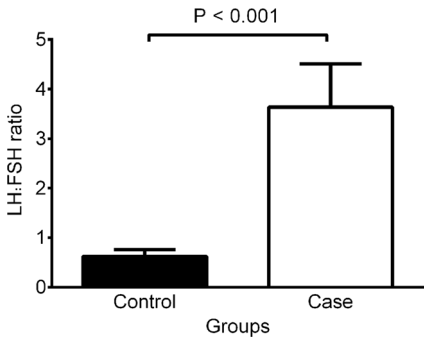

Fig. 2 LH:FSH ratio in 62 healthy women who worked in market without BPA exposure as control group and 62 age- and BMI-matched marketing sellers women with BPA exposure as case group

BPA appears to be elevated in persons with higher body weight and BMI (Rochester 2013); therefore, we selected BMI-matched case and control participants to exclude this interfering effect. In line with our findings, some previous studies reported that women with PCOS had higher serum BPA concentration in comparison to normal healthy control (Barrett and Sobolewski 2014; Kandaraki et al. 2010; Takeuchi et al. 2004; Tsutsumi 2005). For instance, Kandaraki et al. evaluated the BPA levels in PCOS women as well as the association between BPA and hormonal/metabolic parameters compared to a control group. They found higher BPA levels in PCOS women against the control group. In addition, a statistically significant positive relationship between androgens and BPA was detected in PCOS women (Kandaraki et al. 2010). In another study, human contamination of estrogenic endocrine-disrupting chemicals and their risk for human reproduction were investigated. Its results demonstrated that serum BPA concentration was significantly higher in women with PCOS compared with normal women (Tsutsumi 2005). However, there is a report that expressed lack of any associations between PCOS and BPA (Vagi et al. 2014). Possible causes for this disagreement include small sample size and difference in race and age between two groups in their study.

The effects of BPA on thyroid function may be complex. It has been shown that BPA may have both agonistic/antagonistic interactions with the thyroid receptors (Heimeier et al. 2009; Zoeller 2005). TSH is released from the pituitary gland and acts on the thyroid gland to produce tetraidothyronine (T4) and triidothyronine (T3). A negative association between serum TSH concentration and body fluid level of BPA was reported in previous cross-sectional studies on adult subjects (Brucker-Davis et al. 2011; Chevrier et al. 2013; Meeker et al. 2010; Meeker and Ferguson 2011; Wang et al. 2013). Although we found significant lower serum TSH concentration in PCOS women compared to the control healthy group which similar to previous reports but there were

no significant associations between serum TSH concentration and BPA level in each group, separately.

In a recent study, serum concentration of BPA in PCOS and its dependency with liver-spleen axis were evaluated by Tarantino et al (2013). They found that higher BPA levels in PCOS women were associated with higher grades of insulin resistance and hepatic steatosis which were related to dyslipidemia and impaired glucose metabolism. Also, in point of sexual hormone status, it has been reported that PCOS women have higher LH concentration (Rochester 2013) and workers exposed to BPA-diglycidyl ether had significantly lower serum FSH level (Hanaoka et al. 2002). Our findings are in line with the above-mentioned studies but in opposite with Meeker et al., which found that higher urinary BPA was associated with higher FSH, lower inhibin B, higher FSH:inhibin B ratio (Meeker et al. 2010). It seems that in Meeker et al.'s study, the serum BPA level must be decreased due to its urinary secretion and therefore those opposite findings were detected.

Conclusion

In the present study, it has been demonstrated that in market seller women with BPA exposure, the BPA level was higher than age- and BMI-matched healthy women without BPA contact. This difference maybe the cause of significant differences in levels of triglyceride, cholesterol, TSH, and LH:FSH ratio. Higher LH:FSH ratio is an index of PCOS, and these observations confirm the potential role of BPA in PCOS pathophysiology.

Compliance with ethical standards This study strictly followed all of the ethical principles set by the Declaration of Helsinki (2000). The minimum but significant number of participants was allocated for each groups and all participants provided written informed consent. Each participants could finished their cooperation when they want. Also, all efforts were made to minimize pain and harm during blood sampling.

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Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants The aims of the study were clearly discussed for participants and also written consents were obtained from each participant.

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