Letter to the Editor

Association of Bisphenol A Exposure with Circulating Sex Hormone Concentrations in Men and Postmenopausal Women*

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A total of 1 116 middle-aged and elderly men and 1 442 postmenopausal women were recruited in this study. Whether bisphenol A exposure was associated with circulating sex hormone concentrations was studied. Univariate analysis revealed that the urinary bisphenol A concentration was negatively correlated with the serum levels of luteinizing hormone (*β*=-0.061, *P*<0.0001) and follicle-stimulating hormone (*β*=-0.086, *P*<0.0001) in men, and with the serum levels of follicle-stimulating hormone (*β*=-0.037, *P*=0.018) and sex hormone-binding globulin (*β*=-0.043, *P*=0.006) in women. However, no significant association was observed between the serum levels of urinary bisphenol A and circulating sex hormone after adjustment for the potential confounders.

Bisphenol A has been widely used in manufacture of plastics including polycarbonate plastics and epoxy resins that coat food cans and in dental sealants[1-3]. The United States Centers for Disease Control and Prevention reported that bisphenol A is detected in urine from 95% of US adults[4]. It was reported that bisphenol A is associated with various diseases including obesity, cardiovascular disease, type 2 diabetes, low-grade albuminuria and abnormal thyroid function[5-7].

As one of the environmental endocrine disruptors, bisphenol A acts as a metabolic disturber and exerts adverse effects on human health[7-8]. It was reported that bisphenol A has both estrogenic and antiandrogenic effects and may interact with estrogen receptors[7-8]. It has been shown that bisphenol A exposure is related with circulating sex hormone concentrations in both men and women[9-10]. According to one study conducted in 715 adults aged 20 years or older, exposure to a higher bisphenol A level may be associated with a higher total testosterone (TEST) level in men and a higher sex hormone-binding globulin (SHBG) level in premenopausal women[9]. Another study in 167 men revealed that urinary BPA concentrations are negatively associated with the free androgen index (ratio of testosterone to SHBG) and estradiol (E2) level[10]. However, most observations were limited to small sample sizes with more attentions paid to a younger population. The association between urinary bisphenol A concentrations and circulating sex hormone levels was thus studied in this study.

The association between bisphenol A exposure and human health outcomes in Chinese adults was investigated in this cross-sectional study. The study population, design and protocols have been described previously[6]. Briefly, in June-July 2008, a total of 10 185 permanent residents aged ≥40 years in Songnan Community of Shanghai were invited to participate in a screening examination for cardiac metabolic diseases. In June-August 2009, the subjects were randomly selected with their FPG ≥7.0 mmol/L, <7.0 mmol/L, <5.6 mmol/L, respectively. The 3 455 participants were divided into normal glucose regulation (NGR) group, prediabetes group, and diabetes group according to their diabetes history, FPG and OGTT-2h postload plasma glucose (PPG) levels. No significant difference was found in age, sex, and BMI between those included or not included in the cohort.

Those whose serum circulating sex hormone levels were not measured, those who did not

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undergo OGTT and were receiving hormone replacement therapy, and premenopausal women were excluded from the study. Finally, a total of 2 558 participants (1 116 men and 1 442 postmenopausal women) were included in the study.

The participants provided their written informed consent, and the study protocol was approved by The Human Research Committee of RuiJin Hospital, Shanghai Jiaotong University Medical School.

The subjects underwent a 75-g OGTT after an overnight fasting and. Fasting venous blood samples taken for OGTT were immediately centrifuged at 4 °C for 5 min at 4 000 relative centrifugal force. FPG, OGTT-2h PPG and venous plasma glucose levels were measured using the ADVIA-1650 Chemistry System (Bayer Corporation, Germany). Plasma and serum samples were taken and immediately stored in Eppendorf tubes at -80 °C. Circulating sex hormone concentrations, including E2, total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and SHBG, were measured by chemiluminescent microparticle immunoassay and architect assay (Abbott Laboratories, Abbott Park, IL).

Single-void first morning urine samples were taken and stored in 2 bisphenol A-free urine containers. The urinary creatinine concentration was measured in one sample container within 1 h. The other sample was stored at -70 °C within 4 h for the measurement of urinary creatinine concentration using an automatic analyzer (Beckman LX/20, America).

The total urinary bisphenol A concentration was measured in the samples stored at -70 °C within 4 h in Shanghai Institute of Materia Medica, Chinese Academy of Sciences by liquid chromatography-tandem mass spectrometry as previously described[6]. For the BPA concentration <0.30 ng/mL, 0.15 ng/mL was analyzed[6].

Parameters of the 2 558 participants (1 116 males) are presented in Table 1. Their mean age was 61.8 years (SD: 9.5). The median urinary bisphenol A level was 0.94 ng/Ml in men and 0.76 ng/mL in postmenopausal women. The age of males was younger than that of postmenopausal women, and the education level was higher in males than in postmenopausal women (P<0.05). Of the 2 558 participants, 824 (32.2%) suffered from diabetes.

The circulating sex hormone concentrations in the participants are listed in Table 2. The quartile range of urinary bisphenol A was ≤0.57, 0.58-0.94, 0.95-1.71, >1.71 ng/mL in men, and ≤0.43, 0.44-0.76, 0.77-1.40, >1.40 ng/mL in postmenopausal women. The serum levels of LH, FSH, and SHBG were lower in men in the lowest quartile than in postmenopausal women in the highest quartile.

Table 1. Parameters of Participants in This Study

Items	Overall	Men	Postmenopausal Women
N	2 558	1 116	1 442
Bisphenol-A (ng/mL)	0.84 (0.49-1.51)	0.94 (0.57-1.71)	0.76 (0.43-1.40)
Age (y)	61.8±9.5	61.4±9.6	62.1±9.4
Education duration (y)			
≤6	610 (24.4)	152 (13.9)	458 (32.6)
6.1-8.9	1 240 (49.7)	565 (51.8)	675 (48.0)
≥9	646 (25.9)	374 (34.3)	272 (19.4)
Smoking status			
Never smokers	1 834 (71.7)	436 (39.1)	1 398 (97.0)
Ex-smokers	148 (5.8)	133 (11.9)	15 (1.0)
Current smokers	576 (22.5)	547 (49.0)	29 (2.0)
Alcohol consumption			
Never drinkers	2 091 (81.7)	702 (62.9)	1 389 (96.3)
Ex-drinkers	33 (1.3)	32 (2.9)	1 (0.07)
Current drinkers	434 (17.0)	382 (34.2)	52 (3.6)
BMI (kg/m^2)	25.3±3.7	25.1±3.3	25.5±4.0
Waist circumference (cm)	87.6±9.6	89.0±8.8	86.5±10.1
FPG (mmol/L)	5.8±2.0	5.9±2.0	5.8±1.9
OGTT 2h PPG (mmol/L)	10.1±5.7	10.4±5.5	9.9±5.9
Urinary creatinine (μmol/L)	77.1±3.7	76.4±3.7	77.6±3.7
Type 2 diabetes	824 (32.2)	399 (35.8)	425 (29.5)

Note. Data are means±standard deviation or medians (interquartile ranges) or numbers (proportions). BMI: body mass index; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; PPG: postload plasma glucose.

Univariate analysis revealed that the urinary bisphenol A concentration was negatively related with the serum levels of LH (β=-0.061, P<0.0001) and FSH (β=-0.086, P<0.0001) in men, and with the serum levels of FSH (β=-0.037, P=0.018) and SHBG (β=-0.043, P=0.006) in women (Table 3). Multivariate linear regression analysis showed that the urinary bisphenol A concentration was not significantly associated with the circulating sex hormone concentration after adjustment for age, urinary creatinine concentration, education level, cigarette smoking, alcohol consumption, BMI, waist circumference, and OGTT.

The urinary bisphenol A concentration was negatively associated with the serum levels of LH and FSH in men, and with the serum levels of FSH

Table 2. Sex Hormone Concentrations after Bisphenol A Exposure

Variables	Bisphenol A Quartiles (ng/mL)				$P_{\text{for trend}}$
Men	Quartile 1 (≤0.57)	Quartile 2 (0.58-0.94)	Quartile 3 (0.95-1.71)	Quartile 4 (>1.71)	
E2 (pg/mL)	28.84 (25.85-32.17)	30.20 (27.51-33.16)	30.57 (27.80-33.17)	31.00 (28.55-33.67)	0.23
TEST (ng/mL)	3.83 (3.60-4.08)	3.72 (3.53-3.93)	4.00 (3.80-4.20)	3.90 (3.72-4.09)	0.90
LH (mIU/mL)	5.50 (5.08-5.97)	5.68 (5.31-6.08)	5.14 (4.82-5.48)[#]	4.74 (4.46-5.03)[*,#,$]	< 0.001
FSH (mIU/mL)	9.50 (8.64-10.44)	9.21 (8.49-9.97)	7.94 (7.36-8.57)[*,#]	7.54 (7.02-8.10)[*,#]	< 0.001
PRL (ng/mL)	5.50 (5.08-5.96)	5.68 (5.31-6.08)	5.14 (4.82-5.48)[#]	4.74 (4.46-5.03)[*,#]	0.11
SHBG (nmol/L)	45.08 (42.37-47.95)	44.59 (42.30-47.01)	43.61 (42.49-45.84)	42.40 (40.45-44.43)	0.037
Women	Quartile 1 (≤0.43)	Quartile 2 (0.44-0.76)	Quartile 3 (0.77-1.40)	Quartile 4 (>1.40)	
E2 (pg/mL)	17.04 (15.32-18.97)	18.24 (16.26-20.45)	19.87 (17.71-22.28)	19.93 (17.69-22.47)	0.065
TEST (ng/mL)	0.48 (0.46-0.49)	0.50 (0.48-0.52)	0.47 (0.45-0.49)[#]	0.48 (0.46-0.50)	0.51
LH (mIU/mL)	20.61 (19.43-21.86)	20.32 (19.08-21.64)	19.77 (18.56-21.06)	19.67 (18.42-21.00)	0.24
FSH (mIU/mL)	59.93 (56.77-63.26)	56.01 (52.86-59.35)	53.78 (50.76-56.99)[*]	55.11 (51.89-58.53)[*]	0.013
PRL (ng/mL)	10.33 (9.82-10.87)	8.84 (8.35-9.35)[*]	9.06 (8.56-9.59)[*]	9.60 (9.07-10.16)[#]	0.10
SHBG (nmol/L)	58.95 (55.97-62.09)	55.72 (52.61-59.02)	53.37 (50.39-56.52)[*]	52.04 (49.13-55.12)[*]	0.002

Note. Data are medians (interquartile ranges). P for trend are adjusted for urinary creatinine. [*]Compared with Quartile 1 P<0.05; [#]compared with Quartile 2 P<0.05; [$]compared with Quartile 3 P<0.05. Abbreviations: E2: estradiol; TEST: total testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; PRL: prolactin; SHBG: sex hormone-binding globulin.

Table 3. Regression Analysis Showing Bisphenol A and Sex Hormone Levels

Variables	Model 1		Model 2		Model 3	
	β (SE)	P	β (SE)	P	β (SE)	P
Men (n=1 116)						
E2 (pg/mL)	0.028 (0.025)	0.26	0.045 (0.025)	0.07	0.052 (0.027)	0.06
TEST (ng/mL)	0.007 (0.014)	0.64	-0.002 (0.015)	0.89	0.002 (0.014)	0.86
LH (mIU/mL)	-0.061 (0.018)	<0.001	-0.017 (0.017)	0.31	-0.018 (0.017)	0.3
FSH (mIU/mL)	-0.086 (0.021)	<0.001	-0.033 (0.020)	0.1	-0.041 (0.021)	0.06
PRL (ng/mL)	-0.028 (0.017)	0.097	-0.004 (0.017)	0.81	0.003 (0.017)	0.88
SHBG (nmol/L)	-0.026 (0.014)	0.066	-0.001 (0.013)	0.93	0.010 (0.013)	0.44
Postmenopausal Women (n=1 442)						
E2 (pg/mL)	0.055 (0.031)	0.074	0.046 (0.031)	0.15	0.042 (0.032)	0.2
TEST (ng/mL)	0.005 (0.011)	0.67	0.013 (0.010)	0.22	0.008 (0.011)	0.46
LH (mIU/mL)	-0.019 (0.017)	0.27	-0.019 (0.017)	0.26	-0.010 (0.017)	0.58
FSH (mIU/mL)	-0.037 (0.016)	0.018	-0.028 (0.016)	0.072	-0.015 (0.014)	0.32
PRL (ng/mL)	-0.023 (0.015)	0.13	-0.027 (0.016)	0.081	-0.021 (0.016)	0.18
SHBG (nmol/L)	-0.043 (0.016)	0.006	-0.037 (0.016)	0.018	0.010 (0.014)	0.46

Note. Model 1: unadjusted; Model 2: adjusted for urinary creatinine and age; Model 3: further adjusted for BMI, education level, smoking, drinking, waist circumference and diabetes (yes/no) based on Model 2. E2: estradiol; TEST: total testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; PRL: prolactin; SHBG: sex hormone-binding globulin.

and SHBG in postmenopausal women. However, the urinary bisphenol A concentration was not significantly associated with the circulating sex hormone concentration after adjustment for potential confounders.

There was evidence that bisphenol A acts in the pathophysiology of several health outcomes[7-8]. It was reported that bisphenol A disturbs endocrine functions. Even though animal studies showed that bisphenol A is an endocrine disruptor and has an estrogen-mimicking effect, few large-scale epidemiological studies are available on the relation between bisphenol A exposure and circulating sex hormone concentrations.

Recent data from the InCHIANTI study showed that bisphenol A is positively associated with TEST in men[9]. Meeker and his colleagues also showed that bisphenol A is positively associated with TEST in men (P=0.17)[10]. However, no association was found between bisphenol A and TEST in the present study. The InCHIANTI study also found that urinary bisphenol A concentration is significantly associated with a higher SHBG concentration in premenopausal women[9]. Urinary bisphenol A was not significantly associated with SHBG and other sex hormones in this study when the variations in sex hormone secretion in different stages of menstrual cycle were taken into consideration. The present study was conducted in middle-aged or elderly men and postmenopausal women, which indicated that disruption of circulating sex hormone concentrations after bisphenol A exposure may be more significant in a younger population.

The circulating sex hormone concentrations were compared in those with or without diabetes. The serum levels of LH, FSH, PRL, and SHBG were significantly lower in those with diabetes than in those without diabetes. However, no significant difference was found in serum E2 level and total testosterone between those with or without diabetes. Multivariate linear regression analysis showed that the urinary bisphenol A concentration was not significantly associated with the circulating sex hormone concentration in the participants without diabetes after adjustment for age, urinary creatinine concentration, education level, current cigarette smoking, current alcohol consumption, BMI, and waist circumference.

There are some limitations in the present study. First, a causal relation between bisphenol A and circulating sex hormone concentrations could not be concluded due to the cross-sectional nature of the study. Second, the analysis was made according to the bisphenol A concentration in morning urine, which reflected only the recent exposure and might be potentially affected by the intra-individual variations. Third, the results might not be of generality due to the oversampled individuals with diabetes. Finally, the current study was conducted only in postmenopausal women.

In conclusion, bisphenol A exposure is not independently associated with the circulating sex hormone concentration in middle-aged and elderly men and postmenopausal women. Further follow-up studies are warranted to validate our findings.

DISCLOSURE

All the authors declare no competitive interests.

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