Serum bisphenol-A concentration and sex hormone levels in men

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Objective: To evaluate the association between serum bisphenol-A (BPA) concentration and sex hormone levels in men.
Design: Cross-sectional study.
Setting: Not applicable.
Patient(s): A total of 290 men with or without BPA exposure in the workplace.
Intervention(s): None.
Main Outcome Measure(s): Serum sex hormone levels.
Result(s): After adjustment for potential confounders using linear regression, increasing serum BPA concentration was statistically significantly associated with [1] decreased androstenedione levels, [2] decreased free testosterone levels, [3] decreased free androgen index, and [4] increased sex hormone-binding globulin levels. Comparison of hormone levels between workers exposed and unexposed to BPA showed similar associations.
Conclusion(s): Exposure to a high BPA level may impact sex hormone levels in men. (Fertil Steril® 2013;100:478–82. ©2013 by American Society for Reproductive Medicine.)
Key Words: Bisphenol-A, BPA, endocrine disruption, men, sex hormones

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Bisphenol-A (BPA) is one of the world's highest production volume chemicals (1). It is used in the manufacture of polycarbonate plastics and epoxy resins, which can be found in baby bottles, water supply pipes, the lacquer lining of food and beverage containers, dental sealants, carbonless copy paper, and thermal paper in modern cash registers (2–5). BPA can leach from some of these polymers into water or food products (6, 7). It has been reported that BPA can be detected in more than 90% of people in population-representative samples (8–10).

Bisphenol-A is considered to be an endocrine-disrupting chemical with reproductive toxicity (11). Rodent and in vitro studies have suggested that BPA has both estrogenic and antiandrogenic effects (12–14). Studies have reported that BPA exposure is associated with a variety of adverse effects on the male reproductive system including reduced epididymal or testicular sperm counts, worsened sperm motility and velocity, decreased epididymal weight, impaired insulin signaling and glucose homeostasis, decreased steroidogenesis in the testis, and decreased serum follicle-stimulating hormone (FSH) and testosterone levels (15–24). However, these observations were largely based on animal studies or in vitro experiments. Studies of the effect of BPA on the human male reproductive system have been limited. In our previous studies, we observed an increased risk of male sexual dysfunction and reduced sperm quality associated with high BPA exposure (25–27) as well as shortened anogenital distance in male offspring associated with in utero exposure to BPA (28).

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To our knowledge, only six studies from five research teams have examined the relationship between BPA and sex hormones in men. Hanaoka et al. (29) reported that urinary concentrations of BPA were significantly higher in 42 exposed workers than in controls (the same number matched); they also found a mild inverse correlation between urinary BPA level and serum FSH concentrations. Meeker et al. (30, 31) observed urine BPA concentrations were inversely associated with serum inhibin B (INB) levels and positively associated with the FSH level. And inverse relationships between urinary BPA and the free androgen index (FAI) and estradiol (E_2) were found in 167 men recruited through an infertility clinic. Mendiola et al. (32) examined urinary BPA and serum hormones in fertile men and found a significant inverse association between urinary BPA concentration and FAI levels as well as a significant positive association between BPA and sex hormone-binding globulin (SHBG) levels. Galloway et al. (33) found that higher daily BPA excretion was associated with a higher total testosterone concentration in 307 men from the InCHIANTI study. Takeuchi et al. (34) also found significant positive correlations between serum BPA concentrations and total testosterone and free testosterone (FT) levels in 11 men.

To evaluate the association between serum BPA concentration and sex hormone levels in men, we conducted a cross-sectional study among workers who were exposed or not exposed to BPA in the workplace. We measured serum BPA concentrations among all participants, and examined the association between serum BPA and sex hormones, including total testosterone (T), estradiol (E_2), inhibin B (INB), follicle-stimulating hormone (FSH), prolactin (PRL), sex hormone-binding globulin (SHBG), androstenedione (AD), and free testosterone (FT), and the free androgen index (FAI).

MATERIALS AND METHODS

A more detailed description of the study population, recruitment methods, and ascertainment of BPA exposure, health outcomes, and other risk factors can be found elsewhere (26). The study was approved by the institutional review boards of all participating institutions. The following are descriptions of the study methods relevant to the current study.

Study Population

Male workers in a petrochemical company who were exposed to BPA at the workplace for more than 6 months were identified as eligible exposed workers and invited to participate the study. To select subjects without occupational exposure to BPA, male workers whose ages were similar to those of exposed subjects but without any history of occupational BPA exposure were recruited from a tap water factory in the same area. In the current study, a total of 290 male workers agreed to participate in the study among 412 eligible workers. The total participation rate was 61.5%; the participation rate among exposed and unexposed workers was 72.88% and 52.38%, respectively.

Workers who [1] had dental sealant applications or [2] had taken hormonal drugs in the last 1 year, or [3] had received an infertility diagnosis were excluded from the study. All participants gave their written informed consent for participation in the study, including providing blood specimens.

Samples Collection

Venous blood was drawn and collected into an EDTA tube. After retraction of the clot, the samples were centrifuged, and the serum and buffy coat were separated. The serum was stored at −80°C until the analysis was performed.

Serum BPA

Serum BPA was measured by high performance liquid chromatography with a fluorescence detector (HPLC/FLD). The limit of detection (LOD) was 0.39 μg/L. Detailed methods for the assay have been published previously elsewhere (35).

Sex Hormones

Serum total testosterone (T), E_2, INB, FSH, and PRL were measured by magnetic microparticle immune radiation analysis. Sex hormone-binding globulin, AD, and FT were measured by enzyme-linked immunosorbent assay (ELISA). All assays were performed in duplicate. The intra and inter assay variations were both less than 10%. The FAI was calculated as total T × 100/SHBG.

Statistical Analyses

Data analysis was performed using SPSS version 16.0 (SPSS, Inc.). Serum BPA concentrations less than LOD (= 0.39 μg/L) were imputed as LOD divided by the square root of 2 (= 0.276 μg/L), a method used in previous studies (36, 37). Both serum BPA and sex hormone concentrations were log-transformed because of their skewed distribution. Serum BPA and hormone levels (log-transformed) between the exposed and unexposed groups were compared using a t test or analysis of variance (ANOVA). Multiple linear regression analysis was performed to examine the association between serum BPA level and sex hormones after controlling for potential confounders (including age, education, marital status, smoking and alcohol drinking status, history of chronic diseases, and medication history). $P<.05$ (two-sided) was considered statistically significant.

RESULTS

The demographic characteristics of workers exposed and unexposed to BPA are shown in Table 1. The workers exposed and unexposed to BPA were comparable in regard to age, education, marital status, smoking and alcohol consumption, and history of chronic disease.

Almost 71.5% of the serum samples collected from exposed workers had concentrations of BPA >LOD (0.39 μg/L), which was statistically significantly higher than that in unexposed workers (5.2%) (chi-square = 135.40, $P<.001$). Similarly, a statistically significant difference in BPA concentrations was observed between the exposed workers and the unexposed workers (median 3.198 and 0.276 μg/L, respectively) (t = 13.673, $P<.001$). Summary

TABLE 1

Characteristics of workers exposed and unexposed to bisphenol-A.

Variables	Exposed workers n = 137 (%)	Unexposed workers n = 153 (%)	Total n = 290 (%)
Age			
<30	45 (32.8)	51 (33.3)	96 (33.1)
31–40	71 (51.8)	75 (49.0)	146 (50.3)
41–50	17 (12.4)	23 (15.0)	40 (13.8)
>50	4 (3.0)	4 (2.7)	8 (2.7)
Married			
Yes	123 (89.8)	124 (81.0)	247 (85.2)
No	14 (11.2)	29 (19.0)	43 (14.8)
Education			
Junior high or less	22 (16.1)	24 (15.7)	46 (15.9)
Senior high	90 (65.7)	85 (55.6)	175 (60.3)
College or more	25 (16.2)	44 (28.7)	9 (23.8)
History of chronic disease			
Yes	36 (26.3)	30 (19.6)	66 (22.8)
No	101 (73.7)	123 (80.4)	224 (77.2)
Current smoker			
Yes	95 (69.3)	117 (76.5)	212 (73.1)
No	42 (30.7)	36 (23.5)	78 (26.9)
Alcohol consumption			
Yes	34 (24.8)	32 (20.9)	66 (22.8)
No	103 (75.2)	121 (79.1)	224 (77.2)

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statistics for serum hormones concentrations of the exposed and unexposed workers are shown in Table 2.

Concentrations of FSH, PRL, E_2, and T did not differ between the exposed and unexposed workers. However, the levels of AD, FT, and FAI in the BPA-exposed workers were statistically significantly lower than in the unexposed workers (P=.005, .049, .045, respectively). On the other hand, the level of SHBG in the BPA-exposed workers was statistically significantly higher than in the unexposed workers (P=.038). A similar tendency was observed for the INB level, but the difference was of borderline statistical significance (P=.051).

To assess the association between serum BPA concentrations and male sex hormones, we conducted a linear regression analysis among all participants. All linear regression analysis results were adjusted for age, smoking, and alcohol consumption status. There was a statistically significant positive association between serum BPA concentration and SHBG level (β = 0.065; 95% CI, 0.009–0.120). Statistically significant inverse associations were found between the serum BPA concentration and the levels of AD, FT, and FAI (β = −0.070; 95% CI, −0.110 to −0.030; β = −0.049; 95% CI, −0.084 to −0.013; β = −0.073; 95% CI, −0.130 to −0.016, respectively) (Table 3).

DISCUSSION

Our study observed statistically significant inverse associations between serum BPA concentration and serum AD, FT, and FAI levels. The serum BPA concentration was positively associated with the serum SHBG level.

Some animal studies have documented the effect on sex hormone levels of BPA exposure (19–24), but until now similar studies in a human population have been limited. Our previous studies reported that exposure to BPA led to poor semen quality and an increased risk of male sexual dysfunction (25–27). We have also found that parental occupational exposure to BPA during pregnancy was associated with a shortened anogenital distance in male offspring (28). In men, sexual dysfunction and other reproductive abnormalities are often associated with androgen deficiency, but the direct relationship between BPA exposure and male sex hormone levels has not been well examined (29–34).

To our knowledge, ours is the first study to examine the relationship between serum BPA and AD in men. We observed that the serum AD concentration in BPA exposed workers was lower than that in unexposed workers, and the serum BPA concentration was inversely associated with the serum AD level (P=.001). Androstenedione is the precursor of testosterone, acting as an intermediate step in the male biosynthesis pathway that produces testosterone. Decreased AD levels may reduce the conversion to testosterone. An in vitro study of the effect of BPA on steroidogenesis in human H295R cells also observed that BPA exposure could result in decreased production of AD (38).

In our study, we observed a positive association between serum BPA concentration and the serum SHBG level

TABLE 2

Sex hormone levels in workers exposed and unexposed to bisphenol-A.

Hormones M (Q_{25}–Q_{75})	Exposed workers	Unexposed workers	*P* value[a]
FAI	3.090 (1.780–5.180)	3.620 (2.190–5.380)	.045
AD (ng/mL)	2.840 (2.400–4.870)	3.600 (2.540–5.920)	.005
FT (pg/mL)	29.410 (19.120–38.410)	32.580 (26.090–37.670)	.049
SHBG (nM)	41.400 (25.600–57.900)	36.200 (21.000–51.490)	.038
INB (ng/L)	9.690 (6.620–16.900)	8.730 (4.750–14.280)	.051
FSH (mIU/mL)	3.010 (2.130–5.060)	2.920 (1.860–4.375)	.096
PRL (ng/mL)	9.060 (6.240–13.850)	8.350 (5.600–13.930)	.473
E_2 (pg/mL)	38.580 (29.640–51.910)	34.910 (24.350–47.970)	.251
T (ng/mL)	4.330 (3.470–5.240)	4.200 (3.300–5.380)	.992

Note: AD = androstenedione; E_2 = estradiol; FSH = follicle-stimulating hormone; FT = free testosterone; INB = inhibin B; PRL = prolactin; SHBG = sex hormone-binding globulin; T = testosterone.
[a] Using log-transformed hormone levels.

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TABLE 3

Linear regression analysis for hormones and bisphenol-A concentrations.

Hormones	β (95% CI)[a]	P value[a]
FAI	−0.073 (−0.130–0.016)	.012
AD (ng/mL)	−0.070 (−0.110–0.030)	.001
FT (pg/mL)	−0.049 (−0.084–0.013)	.007
SHBG (nM)	0.065 (0.009–0.120)	.023
INB (ng/L)	0.022 (−0.036–0.080)	.454
FSH (mIU/mL)	0.033 (−0.010–0.075)	.130
PRL (ng/mL)	0.026 (−0.012–0.064)	.177
E_2 (pg/mL)	0.008 (−0.028–0.045)	.659
T (ng/mL)	−0.009 (−0.032–0.014)	.456

Note: AD = androstenedione; CI = confidence interval; E_2 = estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; FT = free testosterone; INB = inhibin B; PRL = prolactin; SHBG = sex hormone-binding globulin; T = testosterone.

[a] Using log-transformed bisphenol-A (BPA) concentration and hormone levels.

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(P=.023), which was consistent with previous studies. Mendiola et al. (32) examined urinary BPA and serum hormones in fertile men (n = 302) and found a similar association between BPA and SHBG (β = 0.07; 95% CI, 0.007–0.13) (32). Meeker et al. (31) also found significant positive associations between the BPA concentration and SHBG level using the geometric mean of urine BPA concentrations among 75 men recruited though an infertility clinic (β = 0.07, P=.03). It has been speculated that the increase in SHBG levels is a direct result of the estrogenic action of BPA, because androgen action lowers serum SHBG whereas estrogen action increases it (31).

We also observed an inverse association between the urinary BPA concentration and FAI levels (P=.012). The free androgen index is also considered the measure of bioavailable testosterone and is calculated as the molar ratio of total testosterone to SHBG (39). The results reported by Mendiola et al. (32) and Meeker et al. (31) are consistent with our findings.

In our study, the serum BPA concentration was also inversely associated with the serum FT level (P=.007). Free testosterone, the hormonally active form of testosterone, can interact with cellular hormone receptors. Mendiola et al. (32) found a suggestive inverse correlation between creatinine-adjusted urine BPA concentrations and FT, but the correlation did not reach statistically significance (P=.08) (32). However, Takeuchi and Tsutsumi (34) conducted a small study in men (n = 11) and women (n = 30), and reported positive correlations between the serum BPA concentration and the FT level by use of combined data for men and women (r = 0.609, P<.001) (34, 40). The difference between these studies may be due to differences in population size, gender difference, population source, and sample types.

Serum and urine sampling are the general modalities for biomarkers of environmental exposures. Serum BPA exposure concentration more likely reflects the chronic exposure level whereas urine BPA more likely reflects immediate exposure. Given that the outcomes in our study are hormone levels, which take time to develop, the serum BPA level may be a better biomarker than the urine BPA level for the BPA effect. On the other hand, it has been reported that serum BPA concentrations were on average 42 times lower than urine concentrations (41). Genuis et al. (41) collected blood and urine samples from 20 individuals and analyzed the BPA levels, and found that there were 12 individuals for whom BPA was detected in urine but was undetectable in serum (42). In our previous study, we reported the BPA concentrations of samples from 952 subjects, among whom the detectable rates were 50% for urine samples compared with 17% for serum samples (43). Thus, it is likely that serum BPA may underestimate BPA exposure.

Our study has several limitations. Our sample size is relatively small, and many unexposed workers had BPA levels below the limit of detection. The participation rate was 61.5%, which could be a source of selection bias. We thus evaluated the potential impact of nonparticipation. First, to have participation bias, nonparticipation had to be associated with both sex hormone levels and serum BPA concentration. As the eligible subjects were not likely to know their hormone levels when they decided to participate in the study, it was unlikely that participation was associated with hormone levels. Second, we examined whether nonparticipation was associated with the serum BPA concentration. We had no information about serum BPA concentration for the nonparticipants, but the distributions of age, education level, and employment history (the only information available for the nonparticipants) between the participants and nonparticipants were quite similar. Therefore, it seemed unlikely that the observed association between serum BPA concentration and serum sex hormone level could be explained by participation bias.

In addition, we only had information on BPA and hormone levels through a single serum sample which was collected during the time range of 9:00 AM to 3:00 PM. Considering the daily variations of BPA and hormone level, this may have resulted in some misclassifications of BPA and hormone levels. However, the type of misclassification is likely nondifferential, resulting in attenuation of the observed association. In other words, without the potential misclassification, the observed associations would have been stronger.

CONCLUSION

Our results suggest that serum BPA concentration may be associated with decreased AD, FT, and FAI levels and increased SHBG levels. These findings indicate that exposure to BPA may lead to a reduced level of bioavailable androgen hormones, with a consequent adverse impact on male sexual and reproductive functions. This finding is consistent with previous epidemiologic findings on the association between BPA exposure and reduced semen quality, male sexual function, and genital maldevelopment of male fetuses (25–28). Given the widespread human exposure to BPA, the effect of BPA on the male reproductive system needs to be further examined.

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