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Urinary bisphenol A concentrations are associated with reproductive parameters in young men

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ABSTRACT

Bisphenol A (BPA) is a pervasive environmental toxicant with known reproductive effects on sperm parameters and hormone levels. Several observational studies have investigated the associations between BPA exposure and male reproductive function, but findings are inconsistent. The objective of this study was to assess the associations between urinary BPA concentrations and semen quality and reproductive hormone levels in a cross-sectional study with 215 healthy young university students (18–23 years old), investigated between 2010 and 2011 in Southern Spain (Murcia Region). All subjects provided urine, blood serum and semen samples on a single day. Urinary BPA concentrations were measured by dispersive liquid–liquid microextraction and ultra-high performance liquid chromatography with tandem mass spectrometry detection. Semen quality was evaluated by measuring volume, concentration, motility, morphology and total sperm count (TSC). Serum samples were analyzed for reproductive hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, inhibin B and estradiol. Relationships between urinary BPA concentrations and semen quality parameters and reproductive hormone levels were examined using linear regression, adjusting for potential confounders and covariates. Ninety-five percent of the men had detectable urinary BPA concentrations with unadjusted median (5th–95th) of 2.8 (0.16–11.5) ng/mL. After adjustment for important covariates, there was a significant positive association between urinary BPA concentrations and serum LH levels ($\beta = 0.07$, 95%CI: 0.02;0.12, p-value < 0.01). Urinary BPA concentration was also significantly and inversely associated with sperm concentration ($\beta = -0.04$, 95%CI: −0.07;− 0.02, p-value < 0.01) and TSC ($\beta = -0.05$, 95%CI: −0.08;− 0.02, p-value < 0.01). No significant associations were found between BPA and other semen parameters or reproductive hormone levels. Our results support the hypothesis that BPA exposure may be associated with a reduction in Leydig cell capacity (increased LH levels) and decreased sperm counts in young men.

1. Introduction

Bisphenol A (BPA) is widely used in industry and commerce to manufacture polycarbonate plastics (e.g. water bottles, water storage tanks) and food packaging components (food cans and containers), among other consumer products (CDC, 2008; Vandenberg et al., 2009, 2010). BPA can leak from some of these polymers into water or food products and therefore the main route of exposure is supposed to be through dietary ingestion. BPA is quickly and almost totally excreted via urine (CDC, 2008; Völkel et al., 2002). Several biomonitoring studies around the world have shown that BPA exposure is common among the general population, with detectable concentration in more than 80% of study participants (Calafat et al., 2008; CDC, 2015; Koch et al., 2012).

BPA has been reported to have both estrogenic and anti-androgenic effects through the interaction with estrogen (ER) and androgen (AR)

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receptors (Akingbemi et al., 2004; Lee et al., 2003; Wetherill et al., 2007). In accordance, BPA has recently been shown to reduce testosterone production of cultured human testes explants (Desdoits-Lethimonier et al., 2107). Additionally, numerous toxicological studies have demonstrated that rodents exposed to BPA during peripubertal periods display a significant decrease in testosterone levels (Herath et al., 2004; Richter et al., 2007; Takao et al., 1999) and epididymal sperm counts (Herath et al., 2004). Adult male mice showed a substantial reduction in testicular and epididymal sperm counts, as well serum testosterone levels, following exposure to BPA (Al-Hiyasat et al., 2002; Tohei et al., 2001). However, other studies found no effect of BPA on reproductive parameters in male adult rodents (Ema et al., 2001; Tyl et al., 2002).

A number of studies have investigated the associations between BPA exposure in adulthood and reproductive function in different populations of men (e.g. occupationally exposed to BPA, fertile or potentially infertile, general population or young men unaware of their fecundity), but findings are still conflicting (Chen et al., 2013; Den Hond et al., 2015; Galloway et al., 2010; Goldstone et al., 2015; Kim et al., 2013; Knez et al., 2014; Hanaoka et al., 2002; Lassen et al., 2014; Li et al., 2011; Meeker et al., 2010a, 2010b, 2011; Mendiola et al., 2010; Takeuchi and Tsutsumi, 2002; Vitku et al., 2016; Zhou et al., 2013) (Table 1).

However, to the best of our knowledge, studies exploring associations between exposure to BPA and reproductive function in men non-selected for testicular function or unaware of their fecundity are very scarce. Then, the objective of this study was to assess the relationships between urinary BPA concentrations and semen quality and serum reproductive hormone levels in young men.

2. Material and methods

2.1. Study population

The Murcia Young Men's Study (MYMS) is a cross-sectional study of university students 18–23 years old in the Murcia Region (Southern Spain). Study details are described elsewhere (Mendiola et al., 2013). Briefly, a total of 215 students agreed to participate and completed the study visit between October 2010 and November 2011. At the study visit men underwent an andrological examination, provided semen, urine and blood samples and completed questionnaires on general health and lifestyles. The Research Ethics Committee of the University of Murcia approved this study and written informed consent was obtained from all subjects.

2.2. Semen analysis and physical examination

Semen analyses were carried out as described in detail elsewhere (Mendiola et al., 2013). Briefly, men were asked to abstain from ejaculation for at least 48 h before sample collection. Abstinence time was recorded as the time between current and previous ejaculation as reported by the study subject. Ejaculate volumes were estimated by specimen weight, assuming a semen density of 1.0 g/mL. Sperm concentration was evaluated by hemocytometer (Improved Neubauer; Hauser Scientific, Inc., Horsham, PA, USA). The spermatozoa were classified as either motile or immotile (World Health Organization, 2010) to report the percentage of motile spermatozoa [progressive (PR) and non-progressive (NP)]. Total sperm count (TSC) (volume × sperm concentration) was also calculated. Smears for morphology were made, air-dried, fixed, Papanicolaou stained and assessed using strict criteria (Menkveld et al., 1990). The same specialized biologist carried out all the semen analyses. An external quality control on semen samples throughout the study period was carried out in collaboration with the University of Copenhagen's Department of Growth and Reproduction. Body weight and height were measured using a digital scale (Tanita SC 330-S, London, UK). BMI was calculated as weight in kilograms divided by squared height in meters. The presence of varicocele or other scrotal abnormalities was evaluated and recorded.

2.3. Hormonal analyses

Hormone analysis methods have been described previously (Asklund et al., 2007; Cutillas-Tolín et al., 2015). Briefly, blood samples were drawn from participants' cubital veins on the same time of the day of semen sample collection and were stored and frozen. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone–binding globulin (SHBG) were determined using time-resolved immunofluorometric assays (DELFIA; PerkinElmer, Skovlund, Denmark). Intra- and interassay variations were < 5% in each of the three assays. Serum testosterone levels were determined using a time-resolved fluoroimmunoassay (DELFIA; PerkinElmer) with intra- and interassay variation of < 8%. Estradiol was measured by radioimmunoassay (Pantex, Santa Monica, CA) with an intraassay variation of < 8% and an interassay variation of < 13%. Inhibin b levels were determined by a specific two-sided enzyme immunometric assay (Oxford Bio-Innovation Ltd, Bicester, UK) with intra- and interassay variation of 13% and 18%, respectively. Free testosterone (FT) was calculated using the equation of Vermeulen et al. (1999) assuming a fixed albumin of 43.8 g/L.

2.4. Urinary BPA analyses

Single spot urine samples were used to assess BPA concentrations. First-morning urine samples were collected in 100 mL polypropylene urine collection vessels pretested to ensure that they did not contain or leach any of the compounds under study. All urine samples were frozen at − 80 °C in 4.5 mL polypropylene vials. Samples were sent to the University of Granada (Spain) on dry ice and stored at − 20 °C until analyses were performed.

Analysis of BPA was carried out by dispersive liquid–liquid microextraction (DLLME) and ultra-high performance liquid chromatography with tandem mass spectrometry detection (UHPLC-MS/MS) as previously described with minor modifications (Vela-Soria et al., 2014; Jiménez-Díaz et al., 2016). Briefly, urine samples were thawed completely at room temperature, centrifuged at 2600*g* for 10 min to sediment particulate matter and 0.75 mL were taken to carry out the analysis. In order to determine total BPA amount (free plus conjugated) in urine, each sample was spiked with 50 µL of enzyme solution (β-glucuronidase/sulfatase) and incubated at 37 °C for 24 h. The treated urine was placed in a 15 mL screw-cap glass tube and spiked with 30 µL of the surrogate standard solution (1.25 mg/L of BPA-d_{16}). Urine was diluted to 10.0 mL with 5% NaCl aqueous solution (w/v) and the pH was adjusted to 2.0. Next, 0.75 mL of acetone and 0.75 mL of trichloromethane were mixed and injected rapidly into the aqueous sample with a syringe. After manual shaking, centrifugation and evaporation of the extract, the residue was dissolved with 100 µL of a mixture consisting of water (0.1% ammonia)/acetonitrile (0.1% ammonia), 70:30 (v/v), and finally 10 µL was injected in the LC system. Urinary creatinine concentration (mg/dL) was determined using an automated colorimetric determination based on the Jaffe assay, in the same urine samples in which environmental chemical was assessed. Because of the relatively constant excretion rate of creatinine into the urine (which makes urinary creatinine concentration inversely proportional to urine flow rate), creatinine adjustment is widely used to normalize analyte concentrations in spot samples for environmental exposure monitoring (Barr et al., 2005).

2.4.1. Calibration and quality control

Matrix-matched calibration curves were constructed plotting the analyte/surrogate peak area ratio against the analyte concentration, in synthetic urine (Inn et al., 2001). BPA-d_{16} was used as surrogate. Limit of detection (LOD) obtained was 0.1 ng/mL and limit of quantification (LOQ) was 0.3 ng/mL. Urine samples were extracted in batches of 12,

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