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Urinary concentrations of parabens and reproductive parameters in young men

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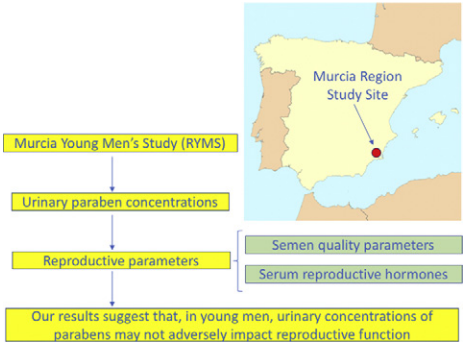
HIGHLIGHTS

- Urinary paraben concentrations were quantified to estimate environmental exposure
- Semen quality and serum reproductive hormone levels were evaluated
- No associations between parabens and any of the reproductive parameters were observed
- Urinary paraben concentrations may not adversely impact male reproductive function

GRAPHICAL ABSTRACT



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ABSTRACT

Parabens are a group of alkyl esters of p-hydroxybenzoic acid that are commonly added to personal care products, cosmetics, pharmaceuticals and beverage and food processing as antimicrobial preservatives. Parabens have been reported to show estrogenic effects and affect male reproduction function in animal models, but human epidemiologic studies are still scarce. The objective of this study was to examine associations between urinary concentrations of parabens and semen quality and reproductive hormone levels. This was a cross-sectional study with 215 young university students (18–23 years old) recruited between 2010 and 2011 in Southern Spain (Murcia Region). All men provided a urine, blood and semen sample on a single day. Urinary paraben concentrations (methylparaben, ethylparaben, propylparaben and butylparaben) 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, sperm concentration, total sperm count (TSC), motility and morphology following WHO guidelines. Serum samples were analyzed for reproductive hormones, including follicle-stimulating hormone, luteinizing hormone, testosterone, inhibin B and

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estradiol using immunoassays. Associations between urinary concentrations of parabens and semen quality parameters and reproductive hormone levels were examined using linear regression, adjusting for potential covariates. Ninety-four percent of the men had detectable urinary concentrations of parabens. After taking into account important covariates, urinary concentrations of parabens or their molar sum were not significantly associated with any semen parameters or any of the reproductive hormone levels. Relative to men in the lowest quartile of sum of urinary paraben concentrations, the adjusted difference (95% CI) of TSC (millions) for men in the 2nd, 3rd, and 4th quartiles were 4.1% (−37.1;45.3), −1.6% (−41.9;38.8), and −9.8% (−52.5;32.8), respectively (P-trend = 0.55). Our results suggest that, in young men, urinary parabens may not adversely impact reproductive function, but further research is warranted to confirm these findings in other male populations.

1. Introduction

Parabens are a group of alkyl esters of p-hydroxybenzoic acid that are commonly added to personal care products, cosmetics, pharmaceuticals and beverage and food processing as antimicrobial preservatives (Andersen, 2008). Widespread human exposure to parabens is through dermal contact, inhalation or ingestion and are excreted via urine (Calafat et al., 2010; Frederiksen et al., 2011; Janjua et al., 2008). International biomonitoring studies have shown that parabens exposure is common among different populations, with detectable concentrations in the urine of most of the people tested (Calafat et el., 2010; CDC, 2015; Moos et al., 2015).

Parabens are thought to have relatively low toxicity (Golden et al., 2005; Soni et al., 2005), and have been reported to show weak estrogenic and anti-androgenic effects in in vitro and animal studies (Chen et al., 2007; Darbre et al., 2008; Gomez et al., 2005; Prusakiewicz et al., 2007; Satoh et al., 2005; Sun et al., 2016; Taxvig et al., 2008). A number of experimental studies have investigated the actions of parabens on male reproductive outcomes, showing that exposure to parabens negatively affects male reproductive system and spermatogenesis in mice or rats (Kang et al., 2002; Oishi, 2002a,b). Conversely, Hoberman et al. (2008) or Oishi (2004) found lack of effect of parabens on reproductive parameters in rodents. Only a very few studies have explored the associations between urinary concentrations of parabens and male reproductive function among humans, thus available information is still scarce. Three cross-sectional studies of male partners of subfertile couples attending infertility clinics examined this question. Meeker et al. (2011) and Nishihama et al. (2017) found no associations between urinary concentrations of parabens and semen parameters or reproductive hormone levels; but recently Jurewicz et al. (2017) reported significant inverse associations between urinary parabens concentrations and sperm morphology and motility and serum testosterone levels. Recently, urinary paraben concentrations were not associated with serum testosterone levels in male adolescents (12–19 years) participating in the National Health and Nutrition Examination Survey (NHANES) 2011–2012 (Scinicariello and Buser, 2016).

However, to the best of our knowledge, there are no studies exploring associations between parabens exposure and reproductive function in men non-selected for testis function or unaware of their fecundity. Therefore, the aim of this study was to assess the associations between urinary concentrations of parabens and semen quality and serum reproductive hormone levels in young men.

2. 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. Physical examination and semen analysis

Body weight and height were measured using a digital scale (Tanita SC 330-S, London, UK). Body mass index (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. 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 to report the percentage of motile spermatozoa [progressive (PR) and non-progressive (NP)] (WHO, 2010). 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.

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) (30) assuming a fixed albumin of 43.8 g/L.