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Associations of fluoride exposure with sex steroid hormones among U.S. children and adolescents, NHANES 2013–2016 ☆

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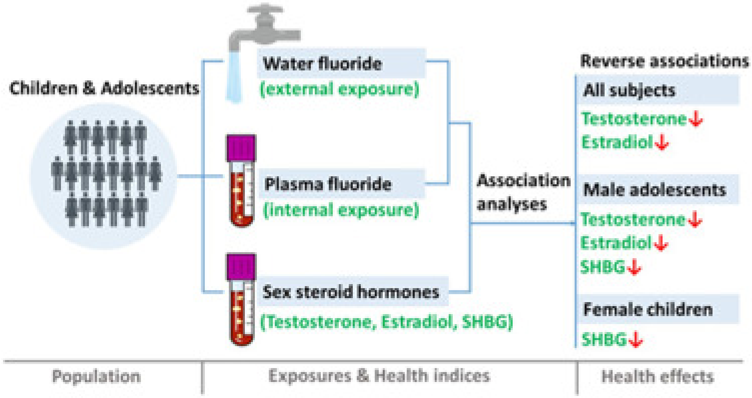
Highlights

- Plasma fluoride is related to lower testosterone and estradiol in male adolescents.
- Water fluoride is inversely associated with SHBG in male adolescents.
- Plasma fluoride is inversely associated with SHBG in female children.

Abstract

Fluoride mediated disruption of sex steroid hormones has been demonstrated in animals. However, evidence from humans was limited and contradictory, especially for children and adolescents. Based on data of the National Health and Nutrition Survey (NHANES) 2013–2016, a total of 3392 subjects aged 6–19 years were analyzed in this cross-sectional study. Both plasma and water fluoride levels were quantified electrometrically using the ion-specific electrode. Sex steroid hormones of total testosterone, estradiol and sex hormone-binding globulin (SHBG) were tested in serum. Percent changes and 95% confidence intervals (CIs) in sex steroid hormones associated with tertiles of fluoride levels (setting the first as reference) were estimated using adjusted linear regression models by stratification of gender and age. Compared with subjects at the first tertile of plasma fluoride, percent changes (95% CIs) in testosterone were −8.08% (−17.36%, 2.25%) and −21.65% (−30.44%, −11.75%) for the second and third tertiles, respectively (P_{trend} <0.001). Male adolescents at the third tertile of plasma fluoride had decreased levels of testosterone (percent change = −21.09%, 95% CIs = −36.61% to −1.77%). Similar inverse associations were also found when investigating the relationships between plasma fluoride and estradiol. Besides, the data indicated decreased levels of SHBG associated with water and plasma fluoride among the male adolescents (percent change of the third tertile = −9.39%, 95% CIs = −17.25% to −0.78%) and female children (percent change of the second tertile = −10.78%, 95% CIs = −17.55% to −3.45%), respectively. The data indicated gender- and age-specific inverse associations of fluoride in plasma and water with sex steroid hormones of total testosterone, estradiol and SHBG in U.S. children and adolescents. Prospective cohort studies are warranted to confirm the causality.

Graphical abstract



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Introduction

Sex steroid hormones play a number of critical roles in reproduction, differentiation, development, cell proliferation, inflammation, metabolism, apoptosis, and brain function (Garcia-Gomez et al., 2013). As the major sex steroid hormones in humans, testosterone and estradiol are mainly synthesized in the gonad, adrenal gland and placenta, and are released into the blood to exert a variety of important functions in sexual differentiation and reproduction, particularly in the development and expression of the secondary sexual characteristics (Garcia-Gomez et al., 2013; Ogino et al., 2018). Sex hormone-binding globulin (SHBG), largely produced by hepatocytes, binds and controls the circulating levels of sex steroid hormones with high affinity (Deswal et al., 2018). As carrier proteins, SHBG regulates the bioavailability, metabolic clearance, and access to target tissues for the sex steroid hormones (Deswal et al., 2018; Ramachandran et al., 2019).

Fluoride is widely distributed in the nature and can be generated from various anthropogenic activities (Jha et al., 2011). To prevent dental decay, more than 200 million people in the United States were served by 18,186 community water systems providing fluoridated drinking water in 2014 (CDC, 2016). Water fluoride was the primary source of U.S. fluoride exposure (Archer et al., 2016). Fluoride intake is regarded as a double-edged sword to human health. Fluoride plays important roles in the bone mineralization and formation of dental enamels, and has beneficial effects when present at low and appropriate levels in drinking water (Jain, 2017; Jha et al., 2011); in contrast, excessive exposure causes health problems of dental fluorosis, osteoporosis, deformation of bones, skeletal fluorosis and inactivation of reproductive organs (Jha et al., 2011; Yadav et al., 2019a; Yadav et al., 2019b). Due to the increased tendency of dental fluorosis, the recommended fluoride level in drinking water was reduced to 0.7 mg/L by the U.S. Public Health Service in 2015 (Health and Human Services Federal Panel on Community Water, 2015). Concerns about the appropriateness of fluoride addition to drinking water had been raised recently (Health and Human Services Federal Panel on Community Water, 2015; Spencer and Do, 2016).

Sex steroid hormones were reportedly highly vulnerable to environmental chemical exposure (Danzo, 1998). Fluoride-induced disruption of sex steroid hormones had been demonstrated in some experimental studies. In zebrafish (Li et al., 2016) and silkworms (Tang et al., 2018), treatment with sodium fluoride was related to altered steroidogenic genes expression, impaired structure of ovary and testis, and reduced levels of testosterone and estradiol. Increased numbers of autophagosomes in testicular tissue, especially in Leydig cells had been observed in fluoride-exposed mice (Zhang et al., 2017). Exposure to sodium fluoride induced a reduction in sperm motility and decreased testosterone levels in male rats and adult men (Ortiz-Perez et al., 2003; Qin et al., 2017). Female rats exposed to fluoride showed structural damage of ovary and uterus, inhibition of follicle maturation, reduced rate of fertility, and decreased levels of testosterone and estradiol (Zhou et al., 2013b).

However, impacts of fluoride exposure on the homeostasis of sex steroid hormones have not been fully characterized in humans, and contradictory data exist in the literature. Up to the present time, several ecological studies have been conducted to compare the concentrations of sex steroid hormones of subjects who were exposed to fluoride at different levels among the occupational workers and farmers (Cui et al., 2013; Duan et al., 2016; Ma et al., 2017; Ortiz-Perez et al., 2003; Zhao et al., 2015; Zhou et al., 2013a), and the clinical patients with skeletal fluorosis (Susheela and Jethanandani, 1996; Tokar and Savchenko, 1977) and polycystic ovary syndrome (Szczuko et al., 2019). Besides, inconsistent findings and crude results without consideration of covariate adjustment [e.g., demographics, smoking, body mass index (BMI)] were reported in the abovementioned ecological studies. Consequently, the generalization of results from the previous studies were inhibited by the limitations in study design and data analyses.

As far as we know, this issue has not been addressed in children and adolescents whose growth of gonad and maturation of reproductive related tissues are regulated by the sex steroid hormones (Hagiuda et al., 2015). The present study was performed to analyze the associations of fluoride in plasma and water with sex steroid hormones including total testosterone, estradiol and SHBG among the general U.S. children and adolescents, respectively.

Section snippets

Study design and participants

The National Health and Nutrition Survey (NHANES), an ongoing cross-sectional survey, is conducted biennially to collect the nationally representative sample in purpose of assessing the heath and nutritional status in the noninstitutionalized U.S. population (CDC, 2017a). Details of the study design, protocols and data collection have been previously reported (CDC, 2017a).

The present study analyzed data from NHANES 2013–2016 in which levels of fluoride in plasma and water samples from the …

Characteristics of subjects

There were 3392 subjects with a mean age of 12.80 years included in the data analyses (Table 1). The number of subjects were 780, 936, 761 and 915, and the mean ages were 8.59, 15.34, 8.62 and 15.35 years for the male children, male adolescents, female children and female adolescents, respectively. The proportions of subjects with serum cotinine levels at or above LLOD were 62.64% among the total sample, and were higher for males compared with females within the same age group (P=0.017). The …

Discussion

To our knowledge, this is the first study to report the relationships between fluoride exposure and sex steroid hormones among the U.S. children and adolescents. The data revealed that levels of plasma and water fluoride were inversely associated with sex steroid hormones of total testosterone, estradiol and SHBG with gender and age specificity, implying possible fluoride-induced disruption in sex steroid hormones and subsequent health problems in growth and development of children and …

Conclusions

In conclusion, our results demonstrated gender- and age-specific inverse associations of plasma and water fluoride levels with one or more sex steroid hormones of total testosterone, estradiol and SHBG in U.S. children and adolescents. Prospective cohort studies are warranted to validate our results in the future. Due to the public concerns of fluoride use and the critical roles of sex steroid hormones, potential public health applications of our findings are substantial. …

Declaration of competing interest

The authors declare no conflict of interest. …

Acknowledgements

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> …More detailed information on laboratory methods can be accessed at the official laboratory method files (CDC, 2018a; 2018b). Several variables were extracted from the NHANES data as confounding factors to build adjusted analysis models following previous papers (Bai et al., 2020; Long et al., 2021; Tao et al., 2021). Because of the known diurnal rhythms and seasonal fluctuations of serum hormones (Diver et al., 2003; Santi et al., 2020), the season and the time of blood collection were also considered as covariates in accordance with previous studies (Bai et al., 2020; Tao et al., 2021).…

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☆ This paper has been recommended for acceptance by Da Chen.

1 Authors contributed equally to this study.

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