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Toxicology

Gender difference in blood cadmium concentration in the general population: Can it be explained by iron deficiency?

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ABSTRACT

Introduction: Gender differences in blood cadmium concentrations and the effect of iron deficiency on blood cadmium levels were analyzed in a representative sample of Koreans assessed in the Korean National Health and Nutritional Examination Survey (KNHANES) 2008–2011.
Methods: A rolling sampling design was used to perform a complex, stratified, multistage probability cluster survey of a representative sample of the non-institutionalized civilian population in South Korea. Serum ferritin was categorized as low (<15.0 μg/L), low normal (15.0–<30.0 μg/L for females and 15.0–<50.0 μg/L for males), and normal (≥30.0 μg/L for females and ≥50.0 μg/L for males), and its association with blood cadmium levels was assessed after adjustment for various demographic and lifestyle factors.
Results: The geometric mean (GM) of the blood cadmium level was significantly higher in females than in males, and significantly higher in older individuals for both genders. After controlling for covariates, multiple regression analysis with interaction terms showed that blood cadmium was correlated with serum ferritin levels only in pre-menopausal females.
Discussion: Iron deficiency is associated with blood cadmium levels in a representative sample of pre-menopausal females, as evaluated in KNHANES. Gender differences in blood cadmium concentration may not be due solely to an iron deficiency-associated increase in blood cadmium.

Introduction

Gender differences in exposure to toxic metals have been reported, but only limited data are available and, with a few exceptions, gender differences in exposure and susceptibility have not been considered in environmental health risk assessments. Although many epidemiological studies have reported data separately for men and women, differences between genders have seldom been evaluated [1–3].

Previous studies have suggested that women retain significantly more cadmium than men, because dietary absorption of cadmium in the intestine increases when iron stores are low [1,4–11]. Cadmium and iron share the same transporter (DMT1), which is required for their absorption and is up-regulated during dietary iron deficiency [12–17]. Thus, pre-menopausal women have higher blood cadmium concentrations than men, and blood cadmium concentrations in women should decrease after menopause. However, reports on blood cadmium concentrations after menopause have been conflicting and inconsistent [18–20]. We therefore assessed gender differences in blood cadmium concentrations and the effect on these concentrations of iron deficiency.

Materials and methods

Design and data collection

This study used data obtained during the Korea National Health and Nutrition Examination Survey (KNHANES) for 2008–2011, representing the second and third years of KNHANES IV (2007–2009) and the first and second years of KNHANES V (2010–2012). KNHANES is conducted annually, using a rolling sampling design that involves a complex, stratified, multistage, probability-cluster survey of a representative sample of the non-institutionalized civilian population in South Korea. Detailed information regarding the

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design of the survey has been reported [21]. Briefly, these surveys consist of three components: a health interview, a health examination, and a nutrition survey.

The present analysis was restricted to participants aged ≥20 years who completed the health examination survey, including heavy metal measurements ($n = 7880$). We included only those who had blood cadmium value and serum ferritin value with liver function value of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). We also excluded individuals who were pregnant, had received treatment for anemia within the last 3 months, had liver cirrhosis or chronic liver diseases, or had chronic renal diseases. Participants with serum ferritin levels >500 μg/L were also excluded. Therefore, the final analytical sample consisted of 7377 participants (females: 3700, males: 3677).

Information on age, education, smoking history, and alcohol intake was collected during the health interview. Height and weight measurements were performed with the participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters and categorized into three groups: lean (BMI < 18.5 kg/m^2), normal (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), and obese (BMI ≥25 kg/m^2). Age, as reported at the time of the health interview, was categorized into ten groups (20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, and ≥65 years). Educational level was categorized into three groups: below high school, high school, and college or higher. Smoking status was divided into three categories based on self-reported cigarette use: current smoker, past smoker, and never-smoker. Never-smokers had smoked <100 cigarettes in their lifetime, and participants who smoked ≥100 cigarettes were classified as past or current smokers based on current use. Alcohol consumption was assessed by asking the participants about their drinking behavior during the month prior to the interview, including their average frequency (days per month) of alcoholic beverage consumption and amount (in mL) of alcoholic beverages ingested on a single occasion. The responses were converted into the amount of pure alcohol (in grams) consumed per day. Alcohol consumption status was categorized into four groups according to average daily alcohol consumption: nondrinkers and light (1–15 g), moderate (16–30 g), and heavy (>30 g) drinkers.

Clinical laboratory assays

Ferritin concentration was measured by an immune radiometric assay method using a 1470 WIZARD gamma-counter (Perkin Elmer, Turku, Finland), and blood hemoglobin was measured with an XE-2100D (Sysmex, Tokyo, Japan).

AST and ALT were measured by a UV method using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan), with each categorized into two groups: normal (AST <40 units/L, ALT <35 units/L) and abnormal (AST ≥40 units/L, ALT ≥35 units/L).

Determination of cadmium in whole blood

To assess cadmium concentrations in whole blood, 3-mL blood samples were drawn into standard commercial evacuated tubes containing sodium heparin for trace-element determination (K2 EDTA tube, Vacutainers), and blood cadmium was measured by graphite furnace atomic absorption spectrometry with Zeeman background correction (Perkin Elmer AAS800, Perkin Elmer). Each sample was analyzed once for blood cadmium by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare. For internal quality assurance and control, three commercial reference materials were used (Lyphochek® Whole Blood Metals Control; Bio-Rad, Hercules, CA, USA), with coefficients of variation within 0.95–4.82% for blood cadmium measurements. As part of external quality assurance and control, the institute passed both the German External Quality Assessment Scheme operated by Friedrich-Alexander University and the Quality Assurance Program operated by the Korea Occupational Safety and Health Agency. The institute was also certified by the Ministry of Employment and Labor as one of the designated laboratories for analysis of specific chemicals, including heavy metals and certain organic chemicals. The limit of detection of blood cadmium using this method was 0.056 μg/L.

Statistical analysis

Statistical analyses were performed using SAS (Version 9.3, SAS Institute, Cary, NC, USA) and SUDAAN (Release 11.0, Research Triangle Institute, Research Triangle Park, NC, USA), a software package that incorporates sample weights and adjusts analyses for the survey's complex sample design. Survey sample weights were used in all analyses to produce estimates that were representative of the non-institutionalized civilian Korean population. To calculate the survey-design adjusted standard errors, Taylor series (linearization) with the WR option were used throughout the analyses.

Blood cadmium concentrations were log-transformed because their distributions were skewed, and the unadjusted geometric means (GMs) [95% confidence interval (CI)] were calculated by gender, age group, residence location, educational level, smoking and drinking status, BMI and menstruation status (for women) using the Proc Descript function in SUDAAN. To compare the GMs of blood cadmium concentrations in different demographic and lifestyle groups while controlling for the above-described covariates, adjusted GMs and 95% CIs were compared using analysis of covariance (ANCOVA), as applied by the Proc Regress function of SUDAAN.

To select an appropriate multiple regression model, we assessed possible interactions of gender on the association between serum ferritin and blood cadmium concentrations using a single model with gender * serum ferritin interaction terms in multiple regression after adjusting for covariates, finding a significant interaction by gender. We further checked the possible interaction of menopausal status on the association between serum ferritin and blood cadmium concentrations using a single model after adjusting for covariates, and found a significant interaction by menopausal status in women. We therefore assessed the possible interaction of three groups (pre-menopausal females, menopausal females, and males) on the association between serum ferritin and blood cadmium concentrations using a single model with three group * serum ferritin interaction terms in multiple regressions after adjusting for covariates, and found a significant interaction among the three groups. We therefore utilized multiple regression analysis for all subjects rather than separately for each of the three groups.

To evaluate whether serum ferritin concentrations were independently associated with blood cadmium concentrations in adults, the logarithmically transformed blood cadmium concentrations were regressed relative to the log-transformed ferritin concentrations after adjustment for age, residence area, smoking and drinking status, educational level, and BMI using multiple regression analysis (Proc Regress, SUDAAN).

Multiple regression analyses were performed after covariate adjustment with the interaction of gender (model 1) and menopausal status in women (model 2) and with the interaction of the three groups of participants and serum ferritin concentration (model 3) in adults aged ≥20 years. In order to provide better understanding of regression coefficient (beta coefficient) in the analysis of multivariate regression analysis using logarithm transformed dependent variable (blood cadmium), we exponentiated the beta

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