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Association between blood cadmium level and bone mineral density reduction modified by renal function in young and middle-aged men

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ABSTRACT

The association between cadmium exposure and bone mineral density (BMD) has not been well studied in young and middle-aged men. This study examined the relationship between the level of blood Cd (BCd) and BMD in a young to middle-aged representative male population while considering renal function. Using data from the 4th Korea National Health and Nutrition Examination Survey, 2008–2009, 1275 adult men aged 20–64 years were analyzed. BCd was measured by atomic absorption spectrophotometry and renal function was assessed by the estimated glomerular filtration rate (eGFR) with CKD-EPI formula. The risk of lower bone density was increased according to the increase in BCd levels after adjusting for eGFR and covariates, in which a significant interaction between BCd and eGFR existed. Significant negative associations between BCd and BMD were found: beta (p-value) were −0.03 (0.02), −0.04 (0.004) and −0.03 (0.04) in total femur, lumbar spine and femoral neck, respectively, which were limited to the people with eGFR ≤ lower 25%. Although, a causal relationship could not be determined because of a cross-sectional design in the present study, the results suggest low level Cd toxicity to bone via low eGFR and that measures to reduce environmental Cd exposure may be helpful to prevent bone loss in men.

1. Introduction

Cadmium (Cd) accumulates gradually in the human body, where it gives rise to a number of adverse health effects, especially nephrotoxicity and bone damage [1–3]. Cd has a biological half-life of 10–30 years within the organ system [4] and sources of Cd exposure in general population are food, tobacco smoke [5], water and polluted air [6,7]. Additionally, long-term exposure to water and food contaminated with Cd, such as rice, leads to health issues and people who live on rice as a staple diet tend to show a high level of Cd concentration [8,9].

It is well known that high level exposure to Cd reduces bone mineral density (BMD) manifesting as osteoporosis and osteomalacia [10,11]. Recently, epidemiological studies reported an association between BMD and low-level environmental Cd exposure, such as osteoporosis-cadmium as a risk factor (OSCAR) [12], Women's Health in the Lund Area (WHILA) of Sweden [13] and Public Health and Environmental Exposure to Cadmium (PheeCad) of Belgium [3]. There have been some arguments on the mechanism of low level environmental Cd exposure and bone density reduction, i.e., direct bone damage, an independent effect of Cd to bone [13,14] and the indirect effect of bone loss through renal damage due to Cd exposure [12,15].

Women are more susceptible to Cd-induced bone loss than men because of frequent opportunities of extensive net loss of bone calcium as occurs during pregnancy and menopause [16], and most previous studies regarding Cd-induced bone loss and fracture have focused on women. Men from an older age group are another susceptible population to Cd-induced renal tubular damage and calcium and bone loss [14]. We limited the study subjects to adult Korean men aged 20–64 years using the representative population data in the present study, to exclude the underlying susceptibility factors of calcium loss from bone commonly observed in females and aged men. We intended to identify whether Cd constituted an environmental risk factor associated with BMD reduction, independently from its mediation of decreased eGFR.

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2. Material and methods

2.1. Study subjects

We used the data from the 4th Korea National Health and Nutrition Examination Survey (KNHANES IV) performed in 2007–2009. The KNHANES surveys have been conducted periodically since 1998 to assess health and a testing for heavy metals in blood was performed during 2008–2009. Among a total of 9213 men participated during 2008–2009, we selected 1275 for analysis after excluding men with less than 20 or 65 or more years old ($n = 4119$), no information of blood cadmium level ($n = 3377$), bone mineral density ($n = 440$) and serum creatinine concentration ($n = 2$).

2.2. Blood cadmium measurement

Whole blood (0.1–0.5 mL) for Cd analysis was put in a trace element EDTA tube and mixed in a stirrer to prevent the formation of froth. The standard addition method was used for the Zeeman correction atomic absorption spectrometer-graphite furnace (GF-AAS) analysis. The blood was added to the matrix modifier reagent (Triton X-100 + ammonium hydrogen phosphate, dibasic + magnesium nitrate + ammonium hydrogen phosphate, mono basic) and blended in a vortex mixer to refine the sample.

Commercial reference materials were used (Lyphochek Whole Blood Metals Control, Bio-Rad, Hercules, CA, USA) for internal quality assurance and control. The coefficients of variation for reference samples in BCd were 1.35–5.29% and 0.97–9.68% in 2008 and 2009, respectively. The limits of detection for blood cadmium were 0.056 and 0.087 μg/L in 2008 and 2009, respectively. No subject had a blood cadmium concentration below the detection limit. 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, as part of external quality assurance and control.

2.3. Renal function

Serum blood urea nitrogen (BUN) was measured by the kinetic UV assay method and serum creatinine (cr) was measured by a kinetic Jaffe method using an auto analyzer (model 7600; Hitachi, Tokyo, Japan). Renal function was assessed using the estimated glomerular filtration rate (eGFR) with CKD-EPI formula. eGFR (mL/min/1.73 m^2) was calculated as as $[141 \times \min(Scr/\kappa, 1)\alpha \times \max(Scr/\kappa, 1)^{)-1.209} \times 0.993^{Age}]$, where Scr is serum creatinine, κ is 0.9, α is −0.411, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [17]. Chronic renal dysfunction was usually defined as subjects with eGFR < 60 mL/min/1.73 m^2 [18], and 13 subjects in the present study belonged to that category. We used the cut point of 89.86 in eGFR for stratification of subjects into 2 groups with lower and higher eGFR, which is the lower 25 percentile of the eGFR distribution in the present study population.

2.4. Bone mineral density (BMD)

Total BMD (g/cm^2) at several areas (whole femur, femoral neck and lumbar spine) was measured using dual-energy X-ray absorptiometry (DXA; DISCOVERY-W fan-beam densitometer; Hologic, Bedford, MA). The stability of DXA measurements was determined by a daily calibration with the phantom supplied from the manufacturer. BMD was graded as a T-score, which refers to a difference between one's BMD and the average BMD of an age group with the highest bone density, measured in units called standard deviations (SD). We used the highest bone density of young Asian adults of the same race (Japan) as reference for the highest bone density (Hologic Discovery, Hologic, USA). According to the WHO criteria, 3 categories of bone mineral density were distinguished: osteoporosis (−2.5 ≥ T-score), osteopenia (−2.5 < T-score ≤ −1), and normal (−1 < T-score) [19]. We defined bone loss (BMD reduction) in the present study as a T-score <−1.

Table 1
Characteristics of 1275 Korean men aged 20–64 years, National Health and Nutrition Survey IV, Korea, 2008–2009.

Variables	
Population characteristics	
No. of subjects	1,275
Age, mean (SE) (years)	40.3 (0.30)
Height, mean (SE) (cm)	171.3 (0.19)
Body mass index, mean (SE) (kg/m^2)	24.2 (0.10)
Education, *N* (%)	
<12 years	264 (17.9)
12 years	555 (45.4)
>12 years	453 (36.7)
Household income, *N* (%)[a]	
Low	142 (10.6)
Low middle	311 (24.7)
Upper middle	392 (32.0)
High	416 (32.7)
Current smoking: yes, *N* (%)	616 (49.2)
Alcohol intake, *N* (%)	
≤1 time (220 cc)/month	284 (22.9)
≥1 time (220 cc)/month	989 (77.1)
Diabetes mellitus: yes, *N* (%)	58 (3.9)
Hypertension: yes, *N* (%)	186 (13.0)
Exercise, *N* (%)	
Inactive	1,073 (84.9)
Active	199 (15.1)
Biomarkers	
Blood cadmium, GM (SE, min, max) (μg/L)[b]	0.83 (1.04, 0.02, 6.04)
Urinary cotinine, GM (SE, min, max) (ng/mL)	59.5 (0.11, 0.01, 7095.40)
Urinary creatinine, GM (SE, min, max) (mg/dL)	166.5 (0.01, 13.10, 563.00)
BUN/cr, mean (SE, min, max)[c]	15.5 (0.15, 5.00, 41.43)
Serum creatinine, mean (SE, min, max) (mg/dL)	0.97 (0.01, 0.58, 8.20)
eGFR, mean (SE, min, max) (mL/min/1.73m^2)[d]	100.5 (0.54, 8.07,145.40)
Bone mineral density (T-score, SD)	
Total femur, mean (SE)	0.42 (0.03)
Lumbar spine, mean (SE)	−0.39 (0.03)
Femoral neck, mean (SE)	−0.02 (0.04)
Bone mineral density reduction	
Total femur, *N* (%)	51 (4.3)
Lumbar spine, *N* (%)	348 (26.9)
Femoral neck, *N* (%)	230 (17.5)

Numbers do not always show the same total because of missing values. Percentages were obtained from chi-square test by survey analysis.

[a] Household income (10^3 KRW/month) classified as low (<1000), low middle (1000–<2000), upper middle (2000–<3000), and high (≥3000).

[b] Level of blood cadmium (ug/L): min = 0.02; 25th = 0.58; 50th = 0.88; 75th = 1.28; max = 6.04.

[c] BUN/creatinine ratio calculated as the concentration of blood urea nitrogen (mg/dL) divided by the concentration of blood creatinine (mg/dL).

[d] eGFR (estimated Glomerular Filtration Rate) (mL/min/1.73 m^2) calculated as $[141 \times \min(Scr/\kappa, 1)\alpha \times \max(Scr/\kappa, 1)^{)-1.209} \times 0.993^{Age}]$, where Scr is serum creatinine, κ is 0.9, α is −0.411, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

2.5. Confounders and covariates

Information on age, household income (low (<1000), low middle (1000–<2000), upper middle (2000–<3000), and high (≥3000), 10^3KRW/month), educational level (below high school (<12 years), high school (12 years) and college or higher (more than 12 years), alcohol consumption during the month prior to interview (≤220 cc drink per month or non-drinker, 220 cc or more drink per month), and exercise (inactive, active (moderate physical activity for at