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Differences in the susceptibility to cadmium-induced renal tubular damage and osteoporosis according to sex

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ABSTRACT

This study aimed to estimate the risks for renal tubular damage and osteoporosis in individuals with long-term environmental Cd exposure. This cross-sectional study comprised 1086 residents living in the vicinity of a copper refinery plant. As the urinary Cd levels increased, the proportion of female subjects with β_2-MG $\geq$300 μg/g creatinine also increased significantly, but this was not observed in the male subjects. The prevalence of osteoporosis was significantly higher in men with urinary Cd >5 μg/g creatinine than in those with urinary Cd $\leq$5 μg/g creatinine. This difference was not observed in the corresponding female groups. The association between increased urinary excretion of β_2-MG and decreased BMD was statistically significant only in the female subjects. We suggest that an increased Cd body burden directly decreases the BMD in male subjects; however, in female subjects, it first induces renal microtubular damage, which can lead to osteoporosis.

1. Introduction

Cadmium (Cd) is a widely distributed metal that is a contaminant in ambient and workplace air as well as in various foods, water, and tobacco. Cd can accumulate in the human body, especially in the bones and kidneys (Hogervors et al., 2007; Schutte et al., 2008).

With a long biological half-life, Cd can induce nephrotoxicity and bone damage. Although Cd-induced bone damage is considered to be caused by nephrotoxicity, which can lead to calcium loss, the mechanism underlying this damage is still

Abbreviations: ANOVA, analysis of variance; BMD, bone mineral density; BMI, body mass index; Cd, cadmium; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GM, geometric mean; β_2-MG, β_2-microglobulin; NAG, N-acetyl-β-D-glucosaminidase; OR, odds ratio; OSCAR, osteoporosis-cadmium as a risk factor.

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not completely understood. The most well-known example is itai-itai disease in Japan (Staessen et al., 1999; Vahter et al., 2002).

Regarding the Cd body burden, Cd is transported to the blood plasma and is bound to metallothionein and albumin, which gives rise to a number of adverse health effects and kidney dysfunction, especially tubular damage, followed by glomerular changes (Chen et al., 2006; Nordberg et al., 1971). The earliest critical manifestation of Cd-induced renal damage is considered to be increased urinary excretion of low-molecular weight proteins such as β_2-microglobulin (β_2-MG) (Chen et al., 2011; Horiguchi et al., 2005). Increased urinary excretion of β_2-MG has been attributed to Cd-induced renal tubular damage (Bernard, 2004; Moriguchi et al., 2009), and a dose-response relationship between Cd level and β_2-MG was found in individuals living in a Cd-exposed area (Kobayashi et al., 2006).

The mechanisms of the toxic effects of Cd on bones are not completely understood, but several possibilities have been suggested. One hypothesis is that Cd primarily induces renal dysfunction, with the following bone damage as a secondary effect. Cd can increase the urinary excretion of calcium and phosphorus and reduce the generation of active vitamin D [1,25(OH)$_2$ D] in the kidneys and the calcium uptake and reabsorption in the gastrointestinal tract (Bernard, 2004; Kimura et al., 1974). It has been also recently reported that environmental Cd exposure at levels insufficient to induce renal dysfunction did not increase the risk of osteoporosis (Chen et al., 2011; Horiguchi et al., 2005). However, other studies have suggested that low-level Cd exposure, which is insufficient to cause kidney damage, might reduce bone mineral density (BMD) and increase the risk of bone damage. Cd-induced demineralization of bone prior to renal dysfunction was identified in some animal studies (Alfvén et al., 2000; Nawrot et al., 2010).

Janghang Copper Refinery, which was established in 1936, smelted copper, lead, and tin until 1989. While it was running, pollutants produced due to the smelting process contaminated soil and water around the refinery. Regarding this Cd contamination, governments discarded all the highly contaminated crops grown near the Janghang Copper Refinery and prohibited farming at this area from 2007. Because of a stream of civil complaints concerning environmental contamination by the refinery, environmental epidemiologic investigations were launched in 2008. The first investigation reported that blood Cd, Cu, and Pb levels, and urinary Cd levels were higher in subjects who lived within 4 km of the refinery than those who lived 15 km or further away. A total of 24.3% of subjects who lived within 4 km of the refinery had blood Cd levels above the reference value (>5 μg/L). Blood Pb levels were below the reference value in all but one subject. No subjects had a Cu level above the reference value.

In the case of Janghang Copper Refinery, subjects who lived closer to the refinery and who had a longer residence period had a higher urinary Cd and urinary β_2-MG levels; this suggested that people in this area had been exposed to high levels of Cd originating from the refinery. Thus, we thought that this population might be ideal as subjects for a long-term Cd toxicity study.

This study aimed to investigate the risk factors for increased urinary β_2-MG excretion and osteoporosis in individuals with long-term exposure to high levels of environmental Cd.

Table 1 – Demographic characteristics of study population.

Variables	Males ($n = 456$)	Females ($n = 630$)
Age (mean ± SD, years)	63.8 ± 11.5	65.2 ± 10.9
BMI (mean ± SD, kg/m^2)	24.1 ± 3.3	25.0 ± 3.5
Urinary Cd level (GM[a] (GSD), μg/g creatinine)	1.6 (2.0)	2.9 (1.9)
Alcohol intake (*N* (%))		
No	182 (39.9)	488 (77.5)
Yes	274 (60.1)	142 (22.5)
Current smoking habit (*N* (%))		
No	129 (28.4)	580 (94.0)
Yes	325 (71.6)	37 (6.0)
Menopause (*N* (%))		
No	–	77 (12.3)
Yes	–	550 (87.7)
Hypertension (*N* (%))		
No	158 (34.7)	225 (35.8)
Yes	298 (65.3)	404 (64.2)
Diabetes (*N* (%))		
No	369 (80.9)	519 (82.4)
Yes	87 (19.1)	111 (17.6)

[a] Geometric mean.

2. Materials and methods

2.1. *Subjects*

Janghang Copper Refinery was founded in Janghang, Seochon, Chungnam Province, Republic of Korea, in 1936, and it was closed in 1989. The study subjects comprised people, aged 30 years or more, who had been living within 4 km of the Janghang Copper Refinery or in a rural area of Seochon located approximately 15 km from the refinery. The mean duration of residence of subjects who lived within 4 km of and further than 15 km from the copper refinery was 39.2 years and 43.9 years, respectively. The mean age of the male and female subjects was 63.8 ± 11.5 and 65.2 ± 10.9 years, respectively. Further, the body mass index (BMI) of the male and female subjects was 24.1 ± 3.3 and 25.0 ± 3.5 kg/m^2, respectively (Table 1). Individuals were given information about the purposes of this study and those who wished to participate then provided written consent and urine samples, thus becoming study subjects. Face-to-face interviews were conducted by experienced interviewers using a standard questionnaire that included demographic questions as well as questions designed to obtain information about history of smoking, alcohol consumption, work history, and specific questions for postmenopausal women. All sampling was carried out in the morning before meal. Blood and urine sample were stored at −80 °C until the day of analysis. There were 1086 study subjects in total (456 men and 630 women).

Height and weight were measured and BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured two or three times during the