Tubular and glomerular kidney effects in the Chinese general population with low environmental cadmium exposure

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HIGHLIGHTS

- Cadmium in urine and blood were positively associated with tubular biomarkers even in children.
- N-acetyl-β-D-glucosaminidase in urine was a very sensitive biomarker of cadmium exposure.
- Cadmium in urine or blood was not associated with a decreased glomerular filtration rate.

ARTICLE INFO

ABSTRACT

Cadmium (Cd), a well-known nephrotoxic agent, has received a great deal of attention from the Chinese public because of reports of its presence in rice. But very few studies have assessed the renal risk of Cd exposure in children. In this cross-sectional study, we aimed to determine whether biologic measures of Cd exposure were associated with biomarkers of early kidney damage in children, adolescents and adults. A total of 1235 subjects (2–86.8 years old) participated in this study and provided samples of blood and urine. As a result, the median urinary Cd level was 0.38 $\mu g \, g^{-1}$ creatinine in adult men and 0.42 $\mu g \, g^{-1}$ creatinine in adult women, similar to reference values observed in the United States (median: 0.32−0.40 $\mu g \, L^{-1}$ in adults). Multiple linear regressions showed Cd in urine to be significantly positively associated with effects on renal tubule biomarkers (as indicated by increased levels of N-acetyl-β-D-glucosaminidase and β2-microglobulin) after adjusting for age, body mass index, blood lead, and urinary density, in all age groups including children. We also found positive associations between blood Cd and renal tubule biomarkers in children. In conclusion, adverse tubular renal effects might have occurred at the current low Cd levels in the study population, including children. These findings are particularly relevant assessing health risks associated with low environmental exposures to Cd.

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1. Introduction

Chronic kidney disease has become an important public health problem in China (Zhang et al., 2012). Cadmium (Cd) is a nephrotoxic metal which is widespread in the environment (Jarup et al., 2000), and is regarded as a possible risk associated with chronic kidney disease (Zhang et al., 2012). Various biomarkers have been used to assess nephrotoxicity among Cd-exposed populations. Elevations in enzymes primarily of renal tubular origin, such as N-acetyl-β-D-glucosaminidase (NAG), have been observed at low levels of environmental Cd exposure in the United States (Noonan et al., 2002). Increases in these enzymes have been associated with chemical-induced renal tubular damage (Goren et al., 1987). Elevations in the excretion of low-molecular-weight proteins, such as β2-microglobulin (BMG), have been used as indicators of damage to the tubular protein absorption capability (Noonan et al., 2002). Low-molecular-weight proteinuria among exposed workers with >10 μg urinary Cd g^{-1} creatinine was irreversible and exacerbated the age-related decline in the glomerular filtration rate (GFR) (Roels et al., 1989). A combination of these biomarkers, which could reflect

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both tubular and glomerular kidney effects, has been used in a previous study (Akesson et al., 2005).

Most studies on the effect of low Cd exposure have focused on adults and especially on older adults (Akesson et al., 2005; Weaver et al., 2014), when the accumulation of Cd in the kidney had reached its peak. Many recent studies have reported Cd exposure in children (Alomary et al., 2013) and even in infants (Sun et al., 2014). However, very few studies assess the renal risk of Cd exposure in children, who are known to absorb metals more readily than adults and are particularly sensitive for biological and developmental reasons (Fels et al., 1998). Furthermore, presently there is no margin between the Cd exposure level in children and the concentration considered to increase the risk of renal tubular damage. Taken together, it was necessary to include children in the study population (de Burbure et al., 2006).

The aim of the present investigation was to study the association between low-level Cd concentrations in the body and a series of markers of tubular and glomerular function in a wide age spectrum of the general population, to assess whether the current level of Cd exposure may be of public health concern. The study was conducted in an area without significant industrial Cd pollution.

2. Materials and methods

2.1. Study site and populations

This study was part of Jiangsu Metal and Health Survey (JMHS), performed in Changshu City, located in east Jiangsu Province in China, which covers a total area of 1264 Km^2 with a residential population of 1.5 million at the end of 2013. We selected an urban community, Changshu City, and five surrounding rural communities as our study area. For each community, 210 subjects were invited to participate in the study, with ages classified as <10, <18, <30, <40, <50, <60, <70 and >70 years. For each age group, we invited 23 to 24 subjects, evenly divided between men and women. The study population in Changshu City comprised local residents aged 2 to 86.8 who had resided at their current address for at least 2 years. A total of 1235 subjects provided signed informed consent and participated this study.

The sample collection was conducted from May 2013 to January 2014. Morning urinary samples (20 ml) were collected at 7 am–8 am and stored in polyacrylamide bottles. Venous blood samples were obtained from the arm of each child in the residential community by registered physicians. Blood samples (~2 mL) were drawn into vacutainers containing K2 EDTA (BD, Franklin Lakes, NJ) and shipped in dry ice to the laboratory of the Jiangsu Provincial Center for Disease Prevention and Control (CDC) for analysis. The weight and height of each participant with light clothing and no shoes or hats were recorded. We designed a structured questionnaire to capture the metal exposure and associated risk factors. The interview questions were divided into three parts: part 1, demographic information and family socioeconomic levels; part 2, food, nutrition, and living habits; and part 3, house and living environment.

This study design was approved by the institutional review board of the Jiangsu Provincial CDC. All participants provided written, informed consent.

2.2. Urinary Cd and blood Cd and lead

The blood samples were obtained from the antecubital vein and collected into vacutainer tubes (2 mL purple top EDTA tubes) for Cd and lead (Pb) measurements (Pb levels were determined in order to find out whether Pb in the investigated blood samples can induce toxic renal effects, besides Cd). The concentrations of Cd and Pb in the collected blood samples and of Cd in the urine samples were measured with an inductively coupled plasma mass spectrometer (ICP-MS; Thermo fisher X-series 2, Houston, TX, USA) using a previously described operating method (Sun et al., 2014). The limit of detection was 0.025 µg L^{-1} for blood Cd, 0.75 µg L^{-1} for blood lead and 0.02 µg L^{-1} for urinary Cd. A total of 25 (25/1235) and 1 (1/1235) participants had blood Cd and lead levels below the limit of detection. For those participants, we assigned a level equal to the limit of detection divided by the square root of 2. For internal quality assurance and control, the Seronorm™ Trace Elements Whole Blood Level-1 (SERO, Norway) standard reference materials were used. The observed values for each element were within the certified range. The recovery was 92% for B–Cd, and 85% for U–Cd. The relative standard deviation (RSD) for both B–Cd and U–Cd were less than 5%. Quality control and assurance procedures included standard reference samples and duplicate detection. The error was less than 8% and the relative standard deviation was within 5% for all samples.

2.3. Measurement of kidney outcomes

Urine samples were analyzed for two biomarkers of tubular damage (NAG and BMG) and for creatinine. Analysis was conducted by the Bio-chemical Laboratory of Changshu CDC, China. We determined NAG in urine by a colorimetric method and determined BMG by a latex enhanced immune-turbidimetric method. We obtained both assay kits from Gcell (Jiuqiang Co. Beijing China) and used an auto-analyzer (model 7180; Hitachi, Tokyo, Japan). We measured serum and urinary creatinine with the kinetic Jaffe method using an auto-analyzer (model 7180; Hitachi, Tokyo, Japan). We used the Modification of Diet in Renal Disease (MDRD) study equation to estimate the glomerular filtration rate (eGFR) as an indicator of glomerular function: eGFR (milliliters per minute per 1.73 m^2) = 175 × (serum creatinine)$^{-1.234}$ × (age)$^{-0.179}$ (× 0.79 if the individual was female). The number of participants with eGFR levels <60 mL min^{-1} per 1.73 m^2 was relatively small (12 men and 31 women). For this study, we categorized participants as having reduced eGFR if their eGFR levels were below the 25th percentile using sex-specific cutoffs (<71.43 mL min^{-1} per 1.73 m^2 for men and <64.83 mL min^{-1} per 1.73 m^2 for women).

2.4. Statistical analysis

All biological parameters are reported as the median and interquartile range (IQR) and were log-transformed to approximate normal distribution. Urinary Cd (U–Cd) and other biomarkers are expressed per liter of urine and per gram of creatinine. We categorized the subjects into three groups: children (age <12), adolescents (age 12–18) and adults (age ≥ 18). The adult group was further divided into six groups by age (as <30, <40, <50, <60, <70, <80, and >80). The level of U–Cd in each age group was compared by ANOVA analysis, with covariables including gender, age, blood Cd (B–Cd), blood lead (B–Pb) and urinary creatinine (U-creatinine). The log U–Cd was compared across gender with log U-creatinine as a covariable by ANOVA analysis followed by an Lsmeans post hoc test. Variations of urinary NAG (U-NAG) and urinary BMG (U-BMG) with U–Cd were modeled using the natural cubic spline function, and we used the TRANSREG procedure of SAS to draw the cubic spline line. The models were run by stratifying the population according to gender.

We assessed the relationship between log U-NAG or U-BMG and a set of independent variables—log U–Cd, sex, age, log B–Cd, log B–Pb, log U-creatinine, body mass index (BMI), family income—in SAS using a Pearson's correlation and multiple linear regression model. At first, we used Pearson's correlation to select variables