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Association of co-exposure to heavy metals with renal function in a hypertensive population

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ABSTRACT

Background: Chronic kidney disease (CKD) is an increasing health problem worldwide. Recent studies have suggested the potential associations between exposure to metals and CKD events, particularly in participants with hypertension. However, relevant studies are limited.

Objectives: We aimed to explore the associations of metal exposure with renal function in participants with essential hypertension.

Methods: Nine hundred and thirty-four participants with essential hypertension were recruited at the Department of Cardiology, Union Hospital, Wuhan, China. We measured the levels of chromium, cadmium, thallium and uranium in urine and calculated the estimated glomerular filtration rate (eGFR) for renal function. Multivariable linear regression models adjusted for potential confounders were applied.

Results: After adjusting for potential confounders and other metals, doubling of urinary chromium or uranium levels decreased eGFR by 2.90 (95% confidence interval, 2.04 to 3.76) and 1.87 (0.58 to 3.15) mL/min per 1.73 m^2, respectively. Co-exposure to chromium and uranium was found to greatly decrease eGFR, particularly in women. Compared with those in the low exposure group, women with high exposure to chromium and uranium had a 11.36 (3.66 to 19.07) mL/min per 1.73 m^2 adjusted decline in eGFR. Higher urinary thallium levels were positively related to elevated eGFR in men. The adjusted increase in eGFR with doubling of thallium levels was 3.12 (1.14 to 5.10) mL/min per 1.73 m^2. Sex-difference in the associations of exposure to heavy metals with eGFR was also suggested.

Conclusions: Our findings suggest that environmental exposure to chromium and uranium might contribute to a decline in eGFR in individuals with hypertension. The associations of exposure to heavy metals with eGFR might be sex-different. Further studies are warranted to confirm our findings and clarify the underlying mechanisms.

1. Introduction

Chronic kidney disease (CKD) is an increasing health problem worldwide (Bello et al., 2005). From 1990 to 2010, global CKD-related age-standardized death rates increased from 9.6 to 11.1 per 100,000 (Lozano et al., 2012). In China, the overall prevalence of CKD was reported to be 10.8%, and the number of CKD patients was estimated to have reached approximately 119.5 million by 2012 (Zhang et al., 2012). Hypertension is a risk factor for CKD. The treatment and prognosis of hypertensive patients have been reported to be strongly affected by kidney involvement (Horowitz et al., 2015). Blood pressure (BP) levels are more difficult to control, and the risks for severe complications increase (Go et al., 2004; Lozano et al., 2012). Cardiovascular diseases are the most common outcomes for hypertension combined with CKD, as well as the major causes of CKD-related mortality (Coresh et al., 2007; Go et al., 2004). There is an urgent need to prevent CKD in hypertensive individuals to avoid complications and improve life quality.

Accumulating evidence has suggested that environmental exposure to heavy metal is a potential CKD risk factor (Akerstrom et al., 2013;

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Barbier et al., 2005b; Sabath and Robles-Osorio, 2012). In the general population, the major routes of environmental exposure to metals occur through the intake of contaminated water and food, air inhalation, or dermal contact (Li et al., 2013; Wu et al., 2014; Zhuang and Gao, 2015). Cadmium is a well-known toxicant with defined nephrotoxicity (Satarug et al., 2010). It can accumulate in the kidney and lead to tubular impairment and renal injury via oxidative stress (Barbier et al., 2005a). Proteinuria, glycosuria, and a reduced glomerular filtration rate (GFR) can result from cadmium exposure even at a low dose (Hwangbo et al., 2011; Satarug et al., 2010). Unlike cadmium, information on the nephrotoxic effects of low-level exposure to other heavy metals is limited. Chromium, thallium and uranium are also heavy metals with potential renal toxicity, with evidence obtained mostly from animal models and occupational exposure studies (Brugge et al., 2005; Cvjetko et al., 2010; Sahu et al., 2014; Stammler et al., 2016; Wang et al., 2011).

Among studies regarding the associations of metal exposure with the risk of CKD events, a clearer and stronger association of metal exposure with kidney events has been observed in participants with hypertension than in those with normal BP. Hypertensive participants with exposure to heavy metals were more likely to have an increased serum creatinine level and a reduced GFR (Kim et al., 2015; Muntner et al., 2003). Metal exposure was found to increase the risk of prevalent albuminuria and β2-microglobulinuria in hypertensive participants but not in normotensive individuals (Liu et al., 2016). Therefore, we hypothesized that individuals might be more vulnerable to the nephrotoxic effect of metal exposure in the presence of high BP levels, leading to renal dysfunction. However, the observed associations might be confounded and amplified by other diseases, such as diabetes and obesity (Lozano et al., 2012; Zhang et al., 2012). In addition, metal studies generally evaluate the unfavorable effect of single metals, but this approach cannot reflect the actual scenarios where people are exposed to multiple metals simultaneously. The interaction effects of co-exposure to multiple metals remain to be clarified. Therefore, we systematically explored the potential nephrotoxic effects of environmental exposure to chromium, cadmium, thallium and uranium at low levels based on a cross-sectional study in patients with essential hypertension for the first time. Estimated GFR was used as the indicator of renal function, and urinary levels of metals were used as the biomarkers of metal exposure.

2. Methods

2.1. Study population

This study, involving 934 hypertensive patients, was conducted from September 2015 to May 2017 in the Union Hospital, Wuhan, China. Participants were consecutively recruited at their first visit to the Department of Cardiology. The hypertension status of the participants was assessed based on the US Seventh Joint National Committee report definition, that is an SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg, or a diagnosis by a physician, or the current use of antihypertensive medication (Chobanian et al., 2003). The existence of essential hypertension was established according to the following criteria: age > 30 years, and no history of diabetes (Alberti and Zimmet, 1998), renal disease (e.g., renal failure, nephrectomy), cerebrovascular disease (e.g., stroke, cerebral infarction), chronic obstructive pulmonary disease and thyroid disease (e.g., hyperthyroidism, hypothyroidism). Participants with potential occupational exposure to metals (n = 20) and incomplete information (n = 32) were excluded. Finally, our study included 934 patients with essential hypertension. Almost all participants were of Chinese Han ethnicity (98.4%). All participants provided written informed consent at enrollment. The research protocol was approved by the ethics committee of the Tongji Medical College, Huazhong University of Science and Technology.

2.2. Data collection

Face-to-face interviews were conducted by a skilled interviewer. Information on socio-economic factors, lifestyle habits, past medical history, medication use, and status of hypertension were collected. Blood pressure measurements were performed by a trained operator as described below (Chen et al., 2015). Briefly, blood pressure measures were taken for three times in a sitting position following a 5-min rest, using a mercury sphygmomanometer, with an appropriately sized cuff placed on the bare right arm. Systolic and diastolic blood pressure (SBP and DBP) measurements were averaged, and pulse pressure (PP) was calculated to be the difference between SBP and DBP. Hypertension-year was defined as the time from the year first diagnosed with hypertension until the examination date.

All participants were requested to provide morning blood and urine samples, following an overnight fast. Urine samples were collected using 50 mL polypropylene containers and frozen at − 20 °C before further analysis. Venous blood samples were centrifuged at 4 °C; serum samples were directly separated and stored at − 80 °C until analysis.

2.3. Urine sample analysis

Urinary metal levels of chromium, cadmium, thallium, uranium and lead were measured using an inductively coupled plasma-mass spectrometer (ICP-MS, NexION™ 300 ×, PerkinElmer Inc., USA). In brief, after centrifugation, 500 μL of supernatant was transferred to 10-mL polypropylene centrifuge tubes and acidified with 20 μL 67% (v/v) HNO_3 (Optima™ grade, Fisher, Belgium) at 5 °C overnight. After the digestion, urine samples were diluted to 5.0 mL with 1% (v/v) HNO_3. The resulting sample was placed first under ultrasound for 30 min and then left to stand at room temperature for a further 30 min before being analyzed. We used the Standard Reference Materials (SRMs) 2670a Toxic Elements in Urine (National Institute of Standards and Technology, NIST) to validate our method (Linsinger, 2005). Additionally, a spiked, pooled sample randomly collected from the study population and SRM 1640a (Trace Elements in Natural Water) were also applied as quality controls. Spiked samples were analyzed for low and high concentrations of each metal to evaluate the method's accuracy. The spiked recovery values of 5 metals ranged from 87.9% to 107.7%, and the within-day and between-day variations were < 10%. A blank sample (1% HNO_3) to ensure the absence of contamination in each batch (20 samples), and an SRM 1640a to assess instrument performance, were analyzed every 20 samples. The limits of detection (LODs) were 0.0141 μg/L, 0.0032 μg/L, 0.0004 μg/L, 0.0003 μg/L, and 0.0021 μg/L for chromium, cadmium, thallium, uranium and lead, respectively. The percentages of study participants with urinary levels below LOD were 5.8%, 0.6%, and 0.9% for chromium, cadmium and uranium, respectively. No sample had urinary levels of thallium and lead below LOD. We assigned the undetected samples a value of one-half the LOD.

The concentrations of urinary creatinine (micrograms per liter, μg/L) were measured to account for urine dilution according to the sarcosine oxidase method on a fully automated clinical chemistry analyzer (Mindray Medical International Ltd.).

2.4. Estimation of kidney function

Serum creatinine levels were measured using the same method as for urinary creatinine. The eGFR was calculated using an adapted equation, derived from the Modification of Diet in Renal Disease (MDRD) equation, based on data obtained from Chinese chronic kidney disease patients, which offered significant advantages in different CKD stages (Ma et al., 2006). The equation based on serum creatinine was as follows: $eGFR = 175 \times Scr^{-1.234} \times age^{-0.179}$ [if female, × 0.79], where Scr is serum creatinine concentration (in mg/dL) and age refers to age in years.