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Urine cadmium levels and albuminuria in a general population from Spain: A gene-environment interaction analysis

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ABSTRACT

Background: The interaction of cadmium with genes involved in oxidative stress, cadmium metabolism and transport pathways on albuminuria can provide biological insight on the relationship between cadmium and albuminuria at low exposure levels.
Objectives: We tested the hypothesis that specific genotypes in candidate genes may confer increased susceptibility to cadmium exposure.
Methods: Cadmium exposure was estimated by inductively coupled plasma mass spectrometry (ICPMS) in urine from 1397 men and women aged 18–85 years participating in the Hortega Study, a representative sample of a general population from Spain. Urine albumin was measured by automated nephelometric immunochemistry. Abnormal albuminuria was defined as urine albumin greater than or equal to 30 mg/g.
Results: The weighted prevalence of abnormal albuminuria was 6.3%. The median level of urine cadmium was 0.39 (IQR, 0.23–0.65) μg/g creatinine. Multivariable-adjusted geometric mean ratios of albuminuria comparing the two highest to the lowest tertile of urine cadmium were 1.62 (95% CI, 1.43–1.84) and 2.94 (95% CI, 2.58–3.35), respectively. The corresponding odds ratios of abnormal albuminuria were 1.58 (0.83, 3.02) and 4.54 (2.58, 8.00). The association between urine cadmium and albuminuria was observed across all participant subgroups evaluated including participants without hypertension, diabetes or chronic kidney disease. We observed Bonferroni-corrected statistically significant interactions between urine cadmium levels and polymorphisms in gene *SLC30A7* and *RAC1*.
Conclusions: Increasing urine cadmium concentrations were cross-sectionally associated with increased albuminuria in a representative sample of a general population from Spain. Genetic variation in oxidative stress and cadmium metabolism and transport genes may confer differential susceptibility to potential cadmium effects.

1. Introduction

Cadmium exposure is widespread, as cadmium can be found in tobacco smoke, some foods (green and root vegetables, grains, shellfish and organ meats) and ambient air (Nordberg et al., 2007). In the general population, the main routes of cadmium exposure include the active or passive inhalation of tobacco smoke, and the oral ingestion of contaminated food and drinking water (US Department of Health and

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Human Services, 2012). Cadmium is a well-established carcinogen and nephrotoxicant (Nordberg et al., 2007; Roels et al., 1989). At high exposure level, cadmium is associated with impaired tubular reabsorption and proteinuria, proximal tubular atrophy, interstitial fibrosis and renal vascular changes (Maruzeni et al., 2014; Nishijo et al., 2006; Nogawa et al., 2004; Prozialeck et al., 2008; Uetani et al., 2007; Yasuda et al., 1995). At low cadmium exposure levels, the association between cadmium and markers of kidney disease is not fully understood. For instance, because cadmium binds to various proteins in serum, it has been argued that urine cadmium concentrations can be related to physiological protein excretion through the glomerulus (Akerstrom et al., 2013; Bernard, 2008).

Abnormal albuminuria concentrations, defined as urine concentrations of albumin greater than or equal to 30 mg/g, can reflect either increased albumin excretion through the glomeruli due to increased endothelial permeability or decreased albumin reabsorption in proximal tubules (Fassett et al., 2011; Redon et al., 2015). Albuminuria is a well-established marker of kidney damage in diabetes and hypertension (Lopez-Giacoman and Madero, 2015). Other causes of albuminuria include primary glomerular disease and kidney damage secondary to systemic diseases. However, these conditions are relatively rare in a population-based setting (McGrogan et al., 2011; Wetmore et al., 2016). In addition, albuminuria is considered as an overall marker of endothelial damage and has been positively associated with increased mortality in several populations (Chronic Kidney Disease Prognosis Consortium et al., 2010; Matsushita et al., 2015; Nitsch et al., 2013; Xu et al., 2007). Few epidemiologic studies have evaluated the association of cadmium with albuminuria at low exposure levels. In non-occupationally exposed populations from the US (geometric mean urinary cadmium 0.22 μg/L (Buser et al., 2016) and geometric mean blood cadmium 0.41 μg/L (Navas-Acien et al., 2009)), China (median urinary cadmium excretion 2.25 μg/L) (Zhang et al., 2015) and Australia (geometric mean urinary cadmium 0.83 μg/g creatinine) (Haswell-Elkins et al., 2008), increasing cadmium levels were consistently associated with increasing albuminuria. Nonetheless, population-based studies from Europe are scarce.

Mechanistic and epidemiologic studies suggest a role of cadmium in altering the redox balance (Jomova and Valko, 2011; Valko et al., 2016). In turn, oxidative stress conditions may promote cadmium toxicity in the endothelium and the kidney. Studies evaluating the interaction of cadmium and genetic variation in genes involved in oxidative stress and cadmium metabolism and transport pathways on albuminuria, however, are scarce. Such gene-environment interaction studies can provide etiological insight into cadmium-associated albuminuria as significant interactions may potentially point to common or inter-related biological pathways. Our objective was, thus, to evaluate the cross-sectional association between urine cadmium and albuminuria in a representative sample of the general population from Valladolid (Spain), and to test the hypothesis that specific genotypes in candidate genes may confer increased susceptibility to cadmium exposure.

2. Methods

2.1. Study population

The Hortega Study is a population-based survey carried out from 1997 to 2003 in adults 15–85 years old assigned to the Rio Hortega University Hospital's health care area in Valladolid (Spain). Participants were selected based on a list of beneficiaries from the universal health care system, which provided a comprehensive representation of the individuals living in the study area (Mena-Martin et al., 2003). In a first step, 20% of the 179,600 individuals included in the registry were randomly selected and invited by mail to participate in the study. The invitation included a questionnaire to collect preliminary information of cardiovascular history and risk factors. The response rate in this step was 33%. In a second step, ~250 participants from each of 6 sex and age-specific strata were selected among individuals who responded to the initial phase of the study to undergo interview and clinical examination and to provide biological samples. In order to guarantee the collection of reliable information participants with serious concomitant diseases or disorders and with mental or social conditions that could complicate or prevent participation in the study were excluded. No exclusions were explicitly made based on kidney disease status of participants. After signing an informed consent form, biological samples were collected and stored, resulting in 1502 participants with available urine for metal determination. 18 participants were excluded due to missing urine cadmium measurements, 4 participants due to missing albumin measurements and 83 participants due to missing other relevant covariates, leaving 1397 participants for this study. The research protocol was approved by ethical committee of the Rio Hortega University Hospital of Valladolid.

2.2. Urine cadmium levels

Urine cadmium levels were measured by inductively coupled plasma mass spectrometry with dynamic reaction cell on an Agilent 7500CEx ICP-OR-MS (Agilent Technologies, United States) following a standardized protocol in the Environmental Bioanalytical Chemistry (AMB) Laboratory at Huelva University (Spain). The lower detection limit for urine cadmium levels was 0.001 μg/L. In the present study, no individual had levels below the detection limit. The intra-assay and inter-assay coefficient variation were 5.2% and 7.2%, respectively.

2.3. Albumin levels

Urine albumin was measured by automated nephelometric immunochemistry (Behring Institute). The limit of detection for urinary albumin was 2.3 mg/L and a total of 471 participants (33.7%) were below the limit of detection. For participants with albuminuria levels below the limit of detection, a concentration equal to the limit of detection divided by the squared root of 2 was imputed (Hornung et al., 1996). The intra-assay and inter-assay coefficient of variation for urine albumin measurement in our laboratory was 2% and 6%, respectively. The ratio of urinary albumin to urinary creatinine (ACR) was reported in milligrams per gram. We defined abnormal albuminuria as an ACR greater than or equal to 30 mg/g.

2.4. Other variables

Information on age, sex, education, smoking status, cumulative exposure to active tobacco smoke (measured as pack-years) and alcohol consumption was based on self-report (Escudero et al., 2003). Body mass index (BMI) was calculated dividing measured weight in kilograms by measured height in meters squared. Urine cotinine was measured by enzyme-linked immunosorbent assay (ELISA) (Kit "Análisis DRI® Cotinina", Ref. 0395 Microgenics laboratories), with a limit of detection of 34 ng/mL (77% of participants below the limit of detection). Participants were considered to have diabetes mellitus if the level of fasting glucose was 126 mg/dL or higher, if hemoglobin A1c was 6.5% or higher, if they had been previously diagnosed of type 2 diabetes by a physician or if they had a record of use of diabetes medications in the clinical history. Blood pressure was measured using a mercury sphygmomanometer. Systolic BP (SBP) and diastolic BP (DBP) were the average of 3 readings measured at 5-min intervals. Urine and serum creatinine were measured by the modified kinetic Jaffé method by isotope dilution mass spectrometry (IDMS) on a Hitachi 917 analyzer (Roche Diagnostics GmbH, Mannheim Germany). The glomerular filtration rate was estimated based on serum creatinine determinations (eGFR) by the CKD-EPI abbreviated formula (Levey et al., 2009).