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Dose-response analysis of environmental exposure to multiple metals and their joint effects with fasting plasma glucose among occupational workers

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HIGHLIGHTS

- The J-shaped dose-response relationships between urinary nickel and zinc with fasting plasma glucose (FPG) were observed.
- A negative linear relationship between urinary cobalt and FPG was found.
- The joint effects between urinary nickel and cobalt with FPG were also observed.
- The shape of relationship should be considered when studying the mechanisms of heavy metal in the pathogenesis of diabetes.

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ABSTRACT

Objectives: Environmental exposure to metals may adversely affect cardiometabolic health. However, little data are available directly evaluating the roles of metal exposure in blood glucose of which dysfunction has been linked to diabetes. We aimed to evaluate the dose-response associations between fasting plasma glucose (FPG) and multiple urinary metals including nickel, cobalt, copper, zinc, and arsenic, as well as to examine their joint effects among occupational workers.
Methods: We performed a population-based study of 464 workers in an ongoing occupational cohort study in China. Both spline and categorical analyses were used to evaluate the dose-response relationship between urinary metals levels and FPG.
Results: We observed the J-shaped non-linear relationships between urinary nickel (P non-linearity $= 0.03$) and zinc (P non-linearity < 0.01) with FPG by spline analyses. A negative linear relationship between urinary cobalt and FPG (P for nonlinearity $= 0.06$) was found, but no statistically significant associations between urinary copper and arsenic with FPG. In linear regression analyses, the regression coefficient for log-transferred FPG was 0.017 (95% confidence intervals [CI]: −0.003, 0.038) in the 4th quartile concentration of urinary nickel, compared with 1st quartile. The joint effects between urinary nickel and cobalt with FPG were also detected (P for interaction $= 0.04$).
Conclusions: Multiple urinary metals, particularly nickel, zinc and cobalt, were associated with blood glucose among Chinese metal exposed workers, supporting the notion that metal exposure may play a critical role in diabetes development.

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1. Introduction

Environmental chemicals may play a role in glucose and lipid homeostasis whose dysfunctions have been linked to diabetes and cardiovascular disease (CVD) (Alissa and Ferns, 2011; Tchounwou et al., 2012). Elevated fasting plasma glucose (FPG) is an independent risk factor for diabetes and has been linked to increased risk of cardiovascular disease (CVD) (Lawes et al., 2004). By the end of 20th century, growing epidemiological studies and evidence including our own had started to link environmental chemicals to diabetes particularly heavy metals (Thayer et al., 2012; Liu et al., 2015; Yang et al., 2015, 2016). However, compared with some well-established risk factors of diabetes such as diet and physical inactivity, the impact of metal exposure on diabetes development is still under-researched, and the evidence for the association of exposure to metals with FPG and diabetes is limited (Kuo and Navas-Acien, 2015).

Among toxic metals, previous epidemiological studies were generally consistent with the association between arsenic (As) exposure and increased risk of FPG or type 2 diabetes (Navas-Acien et al., 2009; Steinmaus et al., 2009; Feng et al., 2015); however, the evidence is not sufficient to infer a causal relationship (Kuo et al., 2013; Kuo and Navas-Acien, 2015). For other metals, the evidence is scare. For example, the first study formally evaluating the association of nickel (Ni) exposure with diabetes risk was reported among Chinese adults by Liu et al. (2015). Interestingly, some heavy metals such as Ni, cobalt (Co), copper (Cu), and zinc (Zn) are also considered as essential nutrients that are involved in various metabolic pathways and biological functions (Fraga, 2005). Both deficiencies and excesses of these elements are frequently related to blood glucose and diabetes (Chen et al., 2009; Feng et al., 2015). Although growing attention is now on the association between heavy metal exposure and risk of diabetes, there is still a huge research gap, such as how to address multiple metal exposures that may be potentially diabetogenic, and whether the shape of dose-response association between urinary metals and FPG is linear or nonlinear.

Metal mining and production industries are one of the largest sources of environmental pollution. A large amount of metals have been released into the environment due to mineral processing activities, which have significant health implications for occupational workers and general populations resulting from environmental pollution. Studies in metal exposed population may be a practical and cost-effective approach to evaluate the impact of metal exposure on diabetes development (Kuo and Navas-Acien, 2015). However, except As, there was very little information on links between Ni and other metals with risk of diabetes in occupational populations or highly exposed levels in general populations (Liu et al., 2016).

The Jinchang Nonferrous Metal Company (JNMC) is located at Jinchang city, Gansu province, China. It is the third largest nickel and second largest cobalt manufacturing enterprise in the world. Workers of the JNMC are routinely exposed to Ni as well as several other metals at high levels that have been measured in urine, such as Co, Cu, As and Zn. The objectives of this study were to comprehensively evaluate the dose-response associations of FPG with multiple urinary metals including Ni, Co, Cu, Zn and As by using both spline and categorical analyses, as well as to examine their joint effects among Chinese metal exposed workers.

2. Materials and methods

2.1. Study population

This study was based on data obtained from the baseline survey of the China metal exposed workers cohort study (Jinchang Cohort), an ongoing perspective cohort study in the Jinchang Nonferrous Metal Industry. The rationale, design, and methods of the cohort have been detailed elsewhere (Bai et al., 2014, 2016). Briefly, we began the baseline survey from June 2011 to December 2013, after which all workers in the cohort participated in medical exams every other year that include in-person interviews, comprehensive physical exams, lab-based tests, and biosample collection. In the current study, a total of 464 occupational workers aged 20–50 years were included, which were randomly selected and matched by sex and age from the specific occupation subgroups (office workers, mining/production workers, and smelting workers) of the Jinchang Industry (Yang et al., 2015). All subjects had given written informed consent and the study protocol was approved by the Ethical Committees of Workers' Hospital of the Jinchang industry and the Ethical Committees of the Public Health School of Lanzhou University.

2.2. Data collection

We collected several types of data in this study including questionnaire data obtained from in-person interviews and clinical data both from physical and biochemical examinations. In-person interviews were conducted by trained interviewers using a standardized questionnaire that included questions pertaining to prior use of tobacco and alcohol, family history of diabetes, medical history, as well as other demographic, socioeconomic, and lifestyle factors. The physical examination was performed by clinicians at the Worker's Hospital of the Jinchang Industry after the completion of the in-person interview. The examination included a measurement of weight, height and blood pressure. Automatical recording instruments (SK-X80/TCS-160D-W/H, Sonka, China) were used to measure weight and height. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Arterial blood pressure was measured three times at the end of the physical examination, with the participant in the seated position after 5 min of rest.

Smoking was categorized as current, former, and non-smoker. Current smokers were defined as those who smoked at least one cigarette per day in the last six months. Former smokers were defined as those who used to be smokers, but who had smoked less than one cigarette per day or stopped smoking for at least the past six months. The rest of the participants were defined as non-smokers. Drinking was categorized as current drinkers who drank hard liquor, beer, or wine at least one time per week during the past six months. Former drinkers were those who used to be drinkers, but who had drank less than one time per week or stopped drinking for at least the past six months. Non-drinkers are those who always drank less than once per week or not at all. Hypertension was defined as systolic $\geq$140 mmHg or diastolic $\geq$90 mmHg, or self-reported treatment for hypertension. Family history of diabetes was defined as having at least one parent, sibling, or offspring with diabetes.

The biochemical examinations were measured using a clinical chemistry automatic analyzer (Hitachi 7600–020, Kyoto, Japan) during the morning, which included fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). The blood glucose levels were measured by the glucose oxidase method. Plasma high-sensitive C-reactive protein (CRP) was measured by latex-enhanced immunoturbidimetric assay (MS-CRP test kit; MediaclSystem, Zhejiang, China). Abnormal lipid measurements were defined as (CDS, 2004): TG $\geq$ 1.70 mmol/L (150 mg/dL) or HDL-C $<$ 0.9 mmol/L (35 mg/dL) in men and $<$1.0 mmol/L (39 mg/dL) in women.