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Multiple metals exposure, elevated blood glucose and dysglycemia among Chinese occupational workers

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ABSTRACT

Aims: Exposure to metals may adversely affect cardiometabolic health. The aim of this study is to directly evaluate the roles of multiple metals exposure in glucose homeostasis, the dysfunction of which has been linked to diabetes and cardiovascular diseases (CVDs).

Methods: We performed a cross-sectional analysis of baseline data from 464 metal-exposed workers who participated in a large prospective occupational study in China (Jinchang Cohort). The logistic regression model was used to evaluate the association between urinary metal levels and high fasting plasma glucose (high-FPG) (≥ 75th percentile) and dysglycemia.

Results: Increasing levels of urinary nickel were prospectively associated with high-FPG: multivariable odds ratios (ORs) were 1.00 for the 1st quartile (lowest), 1.20 (95% confidence interval [CI]: 0.60–2.43) for the 2nd quartile, 1.64 (0.78–3.49) for the 3rd quartile and 3.17 (1.38–7.30) for the 4th quartile (highest) (P-trend = 0.004). The positive associations were also observed between urinary zinc and high-FPG (4th vs. 1st quartile = 2.71, 95%CI: 1.26–5.84, P-trend = 0.01). Inverse associations between urinary cobalt and risk of high-FPG and dysglycemia were observed (P-trend < 0.05). For dysglycemia, the positive trends of increasing levels of urinary nickel and zinc still remained, although urinary nickel was no longer statistically significant. A significant association between urinary arsenic and dysglycemia was also found. However, no associations were observed between urinary copper, cadmium, and risk of high-FPG or dysglycemia.

Conclusion: Multiple urinary metals, particularly arsenic, nickel, zinc, and cobalt, were associated with elevated blood glucose among Chinese occupational workers, supporting the notion that metal exposure plays a critical role in the development of diabetes.

1. Introduction

Exposure to metals may adversely affect cardiometabolic health, although evidence for the association between metal exposure and dysregulation of glucose homeostasis is limited or conflicting (Järup, 2003). Toxic metals, such as arsenic (As) and cadmium (Cd), may play a role in the development of dysglycemia (elevated fasting plasma glucose [FPG], impaired fasting glucose [IFG] and diabetes) (Afridi, Kazi, Kazi, et al., 2008; Chen, Yang, Huang, et al., 2009; Feng, Cui, Liu, et al., 2015). Compared with some well-established risk factors of diabetes, such as diet and physical activity, the impact of metals on diabetes development has been grossly under-researched and their effects possibly underestimated (Kuo & Navas-Acien, 2015).

Some previous studies (Feng et al., 2015; Kuo, Howard, Umans, et al., 2015; Navas-Acien, Silbergeld, Pastor-Barriuso, et al., 2009), but not all (Steinmaus, Yuan, Liaw, et al., 2009; Zierold, Knobeloch, & Anderson, 2004), suggested that exposure to high urinary As level was related to increased risk of type 2 diabetes (T2D), while urinary Cd was inconsistently associated with altered high FPG and IFG (Feng et al., 2015; Swaddiwudhipong, Mahasakpan, Limpatanachote, et al., 2010). Additionally, some heavy metals, including cobalt (Co), copper

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(Cu), nickel (Ni) and zinc (Zn), are also considered 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 T2D risk (Chen et al., 2009; Feng et al., 2015). Specifically, Ni may coexist or interact with other metals, such as As and Cd, which also have been associated with T2D (Liu, Sun, Pan, et al., 2015). However, relatively low exposure in the general population in the U.S. precluded them from being evaluated in relation to T2D risk.

Occupational exposure to metals occurs predominantly in mining, refining, alloy production and welding. However, except As, no information is available on links between other metals and diabetes risk in occupational populations or highly exposed general populations. Recent studies, including our own, have implicated that occupational metal exposures affect T2D risk (Liu, Feng, Wang, et al., 2016; Yang, Cheng, Pu, et al., 2015), but the effects of interactions due to multiple metals exposure were not addressed (Kuo & Navas-Acien, 2015). The Jinchang nonferrous metal industry 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 Jinchang Industry are routinely exposed to nickel as well as several other metals at high levels that have been measured in their urine. At present, little data are available directly evaluating the roles of multiple metals exposure in glucose and lipid homeostasis whose dysfunctions are known pathways to diabetes and cardiovascular diseases (CVDs). The objective of this study was to examine the associations of elevated FPG and dysglycemia with multiple urinary metals, including As, Cd, Co, Cu, Ni and Zn, among those occupational workers.

2. Material and methods

2.1. Study population

This study was based on data obtained from the baseline survey of the Jinchang Cohort Study, an ongoing perspective metal-exposed workers study in the Jinchang Nonferrous Metal Industry. The rationale, design, and methods of the cohort have been detailed elsewhere (Bai, Yang, Pu, et al., 2014). 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 to 50 years were included; they were randomly selected and matched by 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, clinical data 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 T2D, 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. Automatic 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.

The biochemical examinations were measured using a clinical chemistry automatic analyzer (Hitachi 7600-020, Kyoto, Japan) during the morning, which included 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; Medical System, Zhejiang, China).

2.3. Urinary metal assessment

Spot urine specimens were collected in cryogenic tubes, stored at −40 °C, and then shipped on dry ice to the Public Health School of Lanzhou University. Urinary metals were detected using Inductively Coupled Plasma Mass Spectrometry (ICP-MS, Agilent 7700, Agilent Technologies, Santa Clara, CA, USA). All urine samples were coded and analyzed by lab personnel blind to their origin. Each 1 mL of the urine samples was mixed with 3.0% HNO3 to the final volume of 2.5 ml for overnight nitrification. The standard reference material human urine (SRM2670A, National Institute of Standards and Technology, Gaithersburg, MD, USA) was used as an external quality control, and sample spike-recoveries were used to confirm analytical recovery, which was 95%. The intra-day and inter-day coefficient of variation was within 5%. Urine creatinine concentrations were measured by the Sarcosine Oxidase Methods (Suzuki, 1994) with a Mindray BS-200 CREA Kit (Shenzhen Mindray Bio-medical Electronics Co., Ltd., Shenzhen, China).

2.4. Definitions

The outcomes of this analysis included high-FPG and dysglycemia. The cutoff point for high-FPG in this study was determined as 93.6 mg/dL (5.2 mmol/L), which corresponded as the 75th percentile. Dysglycemia was defined as IFG or T2D. IFG was defined as fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L). T2D was defined as fasting plasma glucose ≥126 mg/dL (≥ 7.0 mmol/L) or those who were on anti-diabetic medications at the time of the baseline interview.(Association, 2014) A pack year was defined as twenty cigarettes smoked every day for one year, which is equivalent to 7300 cigarettes smoked(Bernaards, Twisk, Snel, et al., 2001). Current drinker was defined as subject who drank hard liquor, beer, or wine at least one time per week during the past six months. Hypertension was defined as systolic ≥140 mmHg or diastolic ≥90 mmHg, or self-reported treatment for hypertension. Family history of T2D was defined as having at least one parent, sibling, or offspring with T2D. Abnormal lipid measurements were defined as (CDS, 2004): TG ≥ 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.

2.5. Statistical analysis

Descriptive statistics were used to describe the frequency and proportion, mean and standard deviation (SD) of the demographic and clinical characteristics. Logistic regression model was used to test odds ratios (ORs) and confidence intervals (CIs) of high-FPG for each urinary metals quartile compared with the lowest quartile. Tests of linear trend across increasing quartiles of urinary metals were conducted by assigning the medians of metals in quartiles treated as a continuous variable. Basic models were adjusted for other known risk factors for T2D or high-FPG, including age, sex, years of education (<10, 10–12, and >12 years), occupation (office, mining/production, and smelting workers), BMI (<25 or ≥25 kg/m^2), smoking pack-years,