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Early-life arsenic exposure promotes atherogenic lipid metabolism in adolescence: A 15-year birth cohort follow-up study in central Taiwan

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ABSTRACT

Background: Inorganic arsenic (iAs) exposure potentially causes diabetes and cardiovascular diseases in adults. However, its effect on glucose and lipid metabolism in early life remains unknown.
Objective: We evaluated the associations between early-life arsenic exposure and profiles of glucose and lipids in a 15-year birth cohort in central Taiwan.
Methods: We studied 237 adolescents through 5 waves of follow-up interviews and examinations at ages of approximately 2, 5, 8, 11, and 14 y. We obtained at least one follow-up urine measurement for arsenic species and blood sample collection up to 14 y of age and identified group-based trajectories of serial iAs by semi-parametric mixture modeling. Multiple linear and logistic regressions were performed to assess the effect of the arsenic exposure trajectory on serum fasting glucose, total cholesterol (TCHO), triglycerides (TGs), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL).
Results: Three trajectories of postnatal arsenic exposure were identified, namely stable-low (31.4%), stable-high (48.2%), and rising-high (20.4%) groups. Compared with the stable-low trajectory group, the percent changes in TCHO and LDL was 14% (95% confidence interval 4–24%) and 23% (9–38%) for the group with "rising-high" trajectory and was 8% (−1–16%) and 16% (4–29%) for the group with "stable-high" trajectory. The rising-high group was also associated with an increase in the TCHO/HDL ratio by 14% (95% CI 3%–25%). The adjusted odds ratios of high developmental trajectories of TCHO, TG, LDL, and non-HDL levels were 4.0 (95% CI 1.2–13.7), 12.2 (2.2–67), 7.3 (1.8–30), and 3.6 (0.9–14.6), respectively, in the rising-high group (reference: stable-low group).
Conclusion: Our findings suggest that conversion to an atherogenic lipid profile in adolescents may be associated with early-life exposure to environmental arsenic, particularly during the pre-adolescent period. An environmental modification approach for preventing As-related cardiovascular disease is recommended to begin early in life.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death despite considerable therapeutic advancements in cardiovascular intervention and preventive cardiology as well as in integrated health care (Roth et al., 2015; Salisbury et al., 2016). An emerging endemic wave of CVD has been observed among populations in rural, low-income, and middle-income countries that are undergoing rapid epidemiological transitions (Kwan et al., 2016). Finding the earliest possible window to effectively control the development of hypertension and

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atherosclerosis in adulthood is a key priority in global health. An increasing amount of evidence indicates that the atherosclerotic process begins early in life; the latest 2011 guideline funded by National Heart, Lung, and Blood Institute (NHLBI) recommends universal lipid screening in children and adolescents aged 9 to 11 and 17 to 21 y, respectively (Expert Panel on Integrated Guidelines for Cardiovascular et al., 2011; McGill et al., 2000). For children and adolescents with dyslipidemia, particularly those with high levels of atherogenic low-density lipoprotein cholesterol (LDL) and triglycerides (TGs), treatment options are limited to lifestyle changes and dietary interventions; statin therapy is the last resort (Expert Panel on Integrated Guidelines for Cardiovascular et al., 2011). Although debated regarding the causality, environmental hazards have been recognized to contribute the development of atherosclerosis and have attracted much recent attention as environmental factors are more readily modifiable (Cosselman et al., 2015; Ross et al., 2014). For instance, some studies in adult populations have suggested the potential effects of persistent pollutants and lead on lipid metabolism (Lind et al., 2013; Patel et al., 2012; Peters et al., 2012). However, these findings were not conclusive because of the cross-sectional design of those studies and relevant evidence for children and adolescents remains lacking.

Inorganic arsenic (iAs) in water and food is a serious global health concern because of its pervasiveness in the environment, increasing bioavailability in the age of climate change, and well-documented carcinogenicity and atherogenicity in epidemiological research (Argos et al., 2010; Chen et al., 1988; Kibria, 2014). Nevertheless, the exact mechanism underlying As-enhanced atherosclerosis has not been clearly elucidated (States et al., 2009). The most widely accepted etiological theory of arsenic-induced atherogenesis, at in vivo level, is systemic vascular inflammation from arsenic-associated oxidative-antioxidative imbalance, increased endothelial expression of cell-surface adhesion molecules (e.g., soluble intercellular adhesion moelecule-1, sICAM-1), and accumulation of oxidized low-density lipoproteins (oxLDL) that transform the plaque macrophages into lipid-laden foam cells (States et al., 2009). In relation to this, recent in vitro studies have revealed that iAs can down-regulate liver X receptor (LXR) signaling pathway, a key modulator governing intracellular lipid homeostasis involved in lipid trafficking, particularly in macrophage reverse cholesterol transport (RCT) (Hong and Tontonoz, 2014; Janowski et al., 1996; Padovani et al., 2010). This finding is also supported by rodent studies (Cheng et al., 2011; Lemaire et al., 2011). However, it is uncertain how early and whether iAs exposure can alter systemic lipid metabolism. For instance, both in utero and early post-natal (at 3 weeks of age) iAs exposure have been linked to accelerated atherosclerosis in mice studies but plasma lipids were not affected except a significant decrease in TG and large very-low-density lipoprotein (VLDL) particles (Srivastava et al., 2007; Srivastava et al., 2009). In contrast, a study in a rat model revealed significantly higher TG levels and lower ratios of high-density lipoprotein cholesterol (HDL) to LDL among rats exposed to iAs early at 10 weeks of age than those were exposed to iAs late at the age of 24 week with a concomitant high-cholesterol diet (Cheng et al., 2011). This observation is consistent with two recent studies on adult rats that demonstrated significantly elevated levels of TG, LDL, and cholesterol but with a reduced HDL level on low-moderate iAs exposure (Afolabi et al., 2015; Waghe et al., 2017). These observations implied that early-life exposure of arsenic might induce derangement of lipid metabolism, track into adulthood, and increase cardiovascular risk in adulthood. However, to date, evidence from human studies is not available. To fill this critical information gap, we evaluated the associations between the trajectories of serial longitudinal measurements of urinary arsenic and serum lipids levels between urinary arsenic levels and lipoproteins levels among children who were followed up from birth to 15 y of age in Taiwan Maternal and Infant Cohort Study (TMICS) carried out in Taichung City, located in central Taiwan.

2. Methods

2.1. Study population

The TMICS-Taichung is the pilot study of the national TMICS designed to examine the effects of environmental chemicals on maternal and child health. Between December 2000 and November 2001, we invited all healthy pregnant women who received regular prenatal care at a tertiary medical center serving the general population of Taichung City in central Taiwan to participate in this study. The institutional research ethics committee approved this study and all the women provided their written informed consent before participation. In total, we recruited 430 mothers with a mean age of 28.7 y (median 28.9; range, 17–47), and the mean gestational age at enrollment was 33 weeks (range, 4–43). All enrolled women were instructed to complete the demographic and health history questionnaires and provide blood and urine samples in the third trimester of pregnancy. In total, 358 newborn infants were enrolled at birth, and follow-up growth and nutritional assessments including detailed personal interviews. Physical examinations were also conducted along with the collection of blood and urine specimens. Upon reaching elementary school, children who obtained parental permission provided informed consent. The retention rates in the follow-up waves of the children were 53.6%, 45.0%, 42.5%, 39.4%, and 39.9%, respectively, at the ages of 2, 5, 8, 11, and 14 y, respectively (Supplementary Fig. 1). Data of the participants who participated in at least 1 follow-up activity and provided at least 1 urine sample of a sufficient volume for arsenic measurement were analyzed in this study.

2.2. Data collection

In each follow-up wave, trained and certified interviewers administered standardized questionnaires. Physical growth was assessed according to standardized protocols by centrally trained nurses and medical assistants. On the day of return visit, nonfasting blood and random urine samples were collected from the children. During the fifth follow-up wave at the age between 14 and 15 y, we recommended that the participants fast for at least 8 h before blood sample collection. Random urine samples were collected in the polypropylene tubes, frozen within 1–2 h, and transported, buried in dry ice, to the National Health Research Institutes in Taiwan, where they were stored with other blood samples at −70 °C or lower until analysis. The freezers were operated under a strict quality control system to guarantee secure sample storage.

2.3. Lipid profile and insulin resistance measurement

Serum lipid levels were measured using both nonfasting and fasting blood samples using ADVIA 1800 Chemistry System (Siemens Healthcare Diagnostics, IL, USA) with enzymatic colorimetric procedures for the measurements of total cholesterol (TCHO), TG, LDL, and HDL levels. None of these levels were beyond the reportable limits of the analyzer. Across the 15-year follow-up, the same laboratory procedures were used for all samples from the 5 follow-up waves. Glucose levels were also measured using the photometric hexokinase method by using the ADVIA 1800 Chemistry Analyzer. The levels of plasma insulin (μIU/mL) and C-peptide (pmol/L) were also determined using a commercial chemiluminescence system (ADVIA Centaur, Siemens Medical Solutions, Fernwald, Germany).

Fasting homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) was performed using the formulas HOMA-IR = fasting plasma glucose (FPG, mg/dL) × fasting insulin (FI, μIU/mL)/405 and HOMA-β = 360 × FI / (FPG–63), respectively (Matthews et al., 1985). Modified HOMA-IR based on fasting C-peptide level (ng/mL) was also calculated using the following formula: $\text{HOMA-IR}_{\text{C-peptide}}$ = FPG × fasting C-peptide / 2800 (Li et al., 2004). Another