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Association of arsenic with kidney function in adolescents and young adults: Results from the National Health and Nutrition Examination Survey 2009–2012

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ABSTRACT

Background: Long-term exposure to arsenic is a major public health concern. Emerging evidence suggests adverse health effects even at low levels of exposure. This study examined the association of arsenic exposure with estimated glomerular filtration rate (eGFR) and compared methods of adjustment for urinary dilution in a representative sample of U.S. adolescents and young adults.

Methods: We performed a cross-sectional study of 1253 participants ages 12–30 years in the 2009–2012 National Health and Nutrition Examination Survey (NHANES) with available urinary arsenic and eGFR measures. Multivariable linear regression was used to model the association of urinary total arsenic and dimethylarsinate (DMA) with eGFR.

Results: The median urinary total arsenic and DMA concentrations were 6.3 μg/L (IQR 3.3–12.7 μg/L) and 3.3 μg/L (IQR 1.7–5.7 μg/L), respectively. Median eGFR was 109 mL/min/1.73 m^2. Adjusting arsenic for urine concentration with urinary creatinine, eGFR was 4.0 mL/min/1.73 m^2 higher (95% confidence interval [CI] 1.0–7.1 mL/min/1.73 m^2) and 4.3 mL/min/1.73 m^2 higher (95% CI 0.5–8.0 mL/min/1.73 m^2) per log-unit increase in total arsenic and DMA, respectively. When using urine osmolality to adjust for urine concentration, a log-unit increase in total arsenic and DMA was associated with a 0.4 mL/min/1.73 m^2 (95% CI −1.8 to 1.1 mL/min/1.73 m^2) and 0.01 (95% CI −1.9 to 1.9 mL/min/1.73 m^2) lower eGFR, respectively.

Conclusions: Discordant associations were observed between arsenic and eGFR levels depending on whether urinary creatinine or osmolality was used to adjust for urine concentration. Further study should be dedicated to validating the best approach to account for urinary dilution in research in toxicants, and this may have implications for all studies which examine urinary biomarkers.

1. Introduction

Chronic exposure to inorganic arsenic has become a major public health concern throughout the world. Millions of people worldwide are exposed to inorganic arsenic, primarily through contamination of drinking water by natural arsenic deposits (Smedley and Kinniburgh, 2002). The carcinogenic and toxic effects of long-term consumption of water containing high levels of arsenic have been well-described (Chowdhury et al., 2000; Naujokas et al., 2013). The United States (U.S.) Environmental Protection Agency's standard for arsenic concentration in public drinking water supply is 10 μg/L, and approximately 13 million individuals in the U.S. are estimated to live in an area that exceeds this standard (Environmental Protection Agency, 2001).

Humans may be exposed to both organic and inorganic forms of arsenic. Exposure to organic arsenic compounds such as arsenobetaine, primarily via seafood ingestion, is generally considered to be minimally or non-toxic. The complex biotransformation of inorganic arsenic includes detoxification by subsequent methylation into monomethylarsonate (MMA) and dimethylarsenate (DMA) prior to excretion in the urine. Although all metabolites can be measured in the urine, DMA is most frequently detected in urine samples. Methylation is generally

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thought of as a detoxification process; however, some arsenical intermediates in the pathway (especially trivalent inorganic arsenic and MMA) are considered extremely toxic (Agency for Toxic Substances and Disease Registry, 2007). Urinary arsenic excretion has been accepted as an appropriate biomarker of internal dose as urinary arsenic levels are highly correlated to arsenic intake and reflect relatively recent exposures (Centers for Disease Control and Prevention, Fourth Report on Human Exposures to Environmental Chemicals, 2009a). Although some populations with high levels of arsenic exposure (e.g. Bangladesh) have shown some variability in urinary arsenic levels (Kile et al., 2009), a recent analysis of participants in the Strong Heart Study, a population-based study evaluating cardiovascular disease and risk factors in American Indian communities in Oklahoma, Arizona, and North and South Dakota, demonstrated long-term constancy of arsenic exposure and urinary excretion patterns, validating the use of urinary arsenic in large, population-based studies (Navas-Acien et al., 2009).

The kidney is the main organ involved in the excretion of arsenic and its metabolites, and thus several investigations have examined the effect of arsenic poisoning on kidney function. Many studies have examined albuminuria and/or proteinuria as the outcome of interest, as it is often an early marker of glomerular damage and may precede changes in GFR (Zheng et al., 2014). An occupational analysis of 127 male cobalt smelter workers exposed to arsenic trioxide showed an increased prevalence of proteinuria (Liu, 1989). An ecological study performed in southwestern Taiwan, an area of the world with endemic high exposure to arsenic, found a dose–response relationship between levels of inorganic arsenic exposure in well water and kidney cancer prevalence (Chen and Wang, 1990). Furthermore, kidney disease mortality in Taiwan decreased after the installation of public water supply systems and the reduction of arsenic in drinking water (Yang et al., 2004).

To date most investigations of the effects of arsenic on kidney function have been performed in populations with high levels of endemic arsenic exposure. Increasingly the adverse health effects of chronic exposure to low and moderate levels of arsenic (levels in drinking water from <10 to <50 μg/L) have been recognized (Naujokas et al., 2013). An ecological study conducted in southeastern Michigan (median water arsenic, 7.58 μg/L) found a positive association between moderate levels of water arsenic concentrations and kidney disease mortality (Meliker et al., 2007). A cross-sectional analysis of the Strong Heart Study recently found a dose-dependent effect of increasing urinary arsenic concentrations with prevalent albuminuria (Zheng et al., 2013). However, few epidemiological studies have directly examined associations of urinary arsenic with kidney function, and even fewer in young generally healthy populations with a low prevalence of chronic diseases such as diabetes and hypertension which are common causes of decreased kidney function and thus potent confounders. The objective of our study was to examine the association of urinary total arsenic and DMA with markers of kidney function in a representative population of young, generally healthy individuals with low to moderate arsenic exposure.

2. Materials and methods

2.1. Study setting and population

The National Health and Nutrition Examination Survey (NHANES) is a continuous nationally representative multistage random survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) designed to obtain a representative sample of the civilian noninstitutionalized U.S. population. We analyzed combined questionnaire, laboratory, and physical exam data from two survey cycles encompassing 2009–2012. The NHANES study protocols were approved by the institutional review board of the National Center for Health Statistics. Oral and written informed consent was obtained from all participants, or if younger than 18 years, their guardians. Assent was obtained from all those aged 12–17 years. The participation rate in NHANES 2009–2010 was 77.3% and in 2011–2012 was 69.5%.

There were a total of 4647 NHANES participants between the ages of 12 and 30 in the combined 2009–2012 NHANES study. Urinary arsenic measures were obtained on a one-third randomly selected subsample of NHANES participants ($n=1540$) (CDC, 2009b). Of the 1540 eligible participants, 1522 had urinary arsenic measures available. We excluded participants who were pregnant (n=19), missing serum creatinine ($n=129$), measured height ($n=13$), urine osmolality ($n=56$), body mass index (BMI) ($n=3$), or hypertension status ($n=49$), resulting in a final sample size of 1253 participants.

2.2. Urinary arsenic measures

Urine samples were collected from participants at the time of the physical exam in arsenic-free containers and transported on dry ice to the Environmental Health Sciences Laboratory at the National Center for Environmental Health (NCEH: Atlanta, GA) (Caldwell et al., 2009). Urine samples were stored frozen at -70° C or lower and analyzed within 3 weeks of collection according to a standardized protocol (CDC, 2009b). Total urinary arsenic concentrations were measured using inductively coupled-plasma dynamic reaction cell-mass spectrometry on a PerkinElmer ELAN 6100 DRC^{PLUS} or ELAN DRC II ICP-MS (PerkinElmer SCIEX, Concord ON, Canada) (CDC, 2011). Arsenic speciation can distinguish arsenic species that are directly related to inorganic arsenic exposure (arsenate, arsenite, MMA, and DMA) from organic arsenicals in seafood (arsenobetaine, arsenocholine) that are generally considered nontoxic (Fowler et al., 2007). All urinary arsenic species were measured using high performance liquid chromatography (HLPC).

Limits of detection (LOD) and interassay coefficient of variation (CV) differed among analytes and survey cycles. For total arsenic, the detection limit was 0.74 μg/L for the 2009–2010 survey and 1.25 μg/L for the 2011–2012 survey. For the 25 participants (2%) in whom total urinary arsenic levels were below the LOD, values were imputed by a level equal to the LOD divided by the square root of two (CDC, 2009b). The LOD for the 2009–2010 and 2011–2012 cycle was 1.7 and 1.8 μg/L, respectively, for DMA; 0.9 and 0.89 μg/L for MMA; and 0.4 and 1.19 μg/L for arsenobetaine. For the 269 participants (21.6%) with DMA levels and 678 participants (54.4%) with arsenobetaine levels below the LOD their values were similarly assigned a level equal to the limit of detection divided by the square root of two. Although other arsenical metabolites such as arsenate, arsenite, and MMA were measured, they were excluded from this analysis due to the high percentage of undetectable levels (79.1%, 97.4%, and 68.4%, respectively). The interassay CV across NHANES lots ranged from 1.3% to 6.4% for total mean arsenic concentrations, 3.3% to 6.6% for DMA, and 5.3% to 7.3% for arsenobetaine.

2.3. Kidney function measures

Serum and urine creatinine levels were measured by the enzymatic method using a Roche/Hitachi Modular P Chemistry Analyzer which is traceable to an isotope dilution mass spectrometry (IDMS) reference standard. The interassay coefficients of variation ranged from 1.2% to 5.4% for serum creatinine (CDC, 2009d) and 1.4% to 4.4% for urine creatinine (CDC, 2009c).