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Arsenic metabolism and one-carbon metabolism at low-moderate arsenic exposure: Evidence from the Strong Heart Study

Miranda Jones Spratlen [a, *], Mary V. Gamble [b], Maria Grau-Perez [b], Chin-Chi Kuo [c, d], Lyle G. Best [e], Joseph Yracheta [e], Kevin Francesconi [f], Walter Goessler [f], Yasmin Mossavar-Rahmani [g], Meghan Hall [h], Jason G. Umans [i, j], Amanda Fretts [k], Ana Navas-Acien [a, b]

[a] Department of Environmental Health, Johns Hopkins Bloomberg School of Public Health Department, 615 N. Wolfe Street, Baltimore, MD, 21205, USA
[b] Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, 722 W 168th St, New York, NY 10032, USA
[c] Kidney Institute and Division of Nephrology, Department of Internal Medicine, China Medical University Hospital and College of Medicine, China Medical University, No.91, Hsueh-Shih Road, Taichung 40402, Taiwan
[d] Big Data Center, China Medical University Hospital and China Medical University, No. 91, Hsueh-Shih Road, Taichung 40402, Taiwan
[e] Missouri Breaks Industries Research, Inc., 118 S. Willow St, Eagle Butte, SD 57625, USA
[f] Institute of Chemistry - Analytical Chemistry, Universitätsplatz 1/1, 8010 Graz, Austria
[g] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461, USA
[h] Department of Epidemiology, Columbia University Mailman School of Public Health, 722 W 168th St, New York, NY 10032, USA
[i] MedStar Health Research Institute, 6525 Belcrest Rd #700, Hyattsville, MD 20782, USA
[j] Georgetown-Howard Universities Center for Clinical and Translational Science, 4000 Reservoir Road, Washington, DC 20007, USA
[k] Department of Epidemiology, University of Washington, 1959 NE Pacific Street, Health Sciences Bldg, F-262 Box 357236, Seattle, WA 98195, USA

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ABSTRACT

B-vitamins involved in one-carbon metabolism (OCM) can affect arsenic metabolism efficiency in highly arsenic exposed, undernourished populations. We evaluated whether dietary intake of OCM nutrients (including vitamins B2, B6, folate (B9), and B12) was associated with arsenic metabolism in a more nourished population exposed to lower arsenic than previously studied. Dietary intake of OCM nutrients and urine arsenic was evaluated in 405 participants from the Strong Heart Study. Arsenic exposure was measured as the sum of iAs, monomethylarsonate (MMA) and dimethylarsenate (DMA) in urine. Arsenic metabolism was measured as the individual percentages of each metabolite over their sum (iAs%, MMA%, DMA%). In adjusted models, increasing intake of vitamins B2 and B6 was associated with modest but significant decreases in iAs% and MMA% and increases in DMA%. A significant interaction was found between high folate and B6 with enhanced arsenic metabolism efficiency. Our findings suggest OCM nutrients may influence arsenic metabolism in populations with moderate arsenic exposure. Stronger and independent associations were observed with B2 and B6, vitamins previously understudied in relation to arsenic. Research is needed to evaluate whether targeting B-vitamin intake can serve as a strategy for the prevention of arsenic-related health effects at low-moderate arsenic exposure.

1. Introduction

Inorganic arsenic (iAs) in food and water is a major global health concern. An established carcinogen, chronic arsenic exposure also increases the risk of cardiovascular disease, respiratory disease, neurologic deficits, and diabetes(Chen et al., 2011; Council, 2001; Kuo et al., 2013; Moon et al., 2012; Naujokas et al., 2013; Tyler and Allan, 2014; Wu et al., 2014). After ingestion, iAs (arsenate and arsenite) is metabolized into mono- and di-methylated

* Corresponding author. Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Room W7015, Baltimore, MD, 21218, USA.
E-mail addresses: mjones47@jhu.edu (M.J. Spratlen), mvg7@cumc.columbia.edu (M.V. Gamble), mg3749@cumc.columbia.edu (M. Grau-Perez), chinchik@gmail.com (C.-C. Kuo), lbest@restel.com (L.G. Best), joseph.yracheta@mbiri.com (J. Yracheta), kevin.francesconi@uni-graz.at (K. Francesconi), walter.goessler@uni-graz.at (W. Goessler), yasmin.mossavar-rahmani@einstein.yu.edu (Y. Mossavar-Rahmani), mh2825@cumc.columbia.edu (M. Hall), jason.umans@gmail.com (J.G. Umans), amfretts@u.washington.edu (A. Fretts), an2737@cumc.columbia.edu (A. Navas-Acien).

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Abbreviations

Arsenic Metabolism Principal Component 1 As PC 1
Arsenic Metabolism Principal Component 2 As PC 2
Body Mass Index BMI
Chronic Kidney Disease Epidemiology Collaboration CKD-EPI
Dietary Folate Equivalent DFE
Dimethylarsenate DMA
Estimate Glomerular Filtration Rate eGFR
Food Frequency Questionnaire FFQ
High Performance Liquid Chromatography/Inductively Coupled Plasma-Mass Spectrometry HPLC/ICPMS
Inorganic Arsenic iAs
Monomethylarsonate MMA
One-Carbon Metabolism OCM
One-Carbon Metabolism Principal Component 1 OCM PC 1
One-Carbon Metabolism Principal Component 2 OCM PC 2
One-Carbon Metabolism Principal Component 3 OCM PC 3
One-Carbon Metabolism Principal Component 4 OCM PC4
Principal Component Analysis PCA
Randomized Controlled Trial RCT
Total arsenic $\sum$As

arsenicals (MMA and DMA); DMA has a shorter circulating half-life and is more rapidly excreted through the urine as compared to iAs(Aposhian and Aposhian, 2006; Challenger, 1951; Cullen WR, 1989; Hayakawa et al., 2005; Naranmandura et al., 2006; Vahter, 2002). The urinary distribution of arsenic metabolites across human populations ranges from 10-30% for iAs, 10–20% for MMA and 60–80% for DMA(Chiou et al., 1997; Del Razo et al., 1997; Hopenhayn-Rich et al., 1996; Navas-Acien et al., 2009; Vahter, 2000). Higher percentages of iAs (iAs%) and MMA (MMA%) and lower percentages of DMA (DMA%) in urine are thought to reflect a less efficient arsenic metabolism profile and have been associated with higher risk of cancer, skin lesions and cardiovascular disease(Chen et al., 2003a, 2003b, 2005; Del Razo et al., 1997; Hsueh et al., 1997; Steinmaus et al., 2006; Wu et al., 2006; Yu et al., 2000). Conversely, higher DMA% and lower MMA% have been associated with diabetes, metabolic syndrome and higher body mass index(Chen et al., 2012; Del Razo et al., 2011; Kuo et al., 2015; Mendez et al., 2016; Nizam et al., 2013; Wang et al., 2007). Understanding non-modifiable (genetics, sex, life-stage) and modifiable (smoking, alcohol intake, kidney function, body mass index, nutrition) determinants of arsenic metabolism is important given the role of arsenic metabolism in arsenic toxicity(Balakrishnan et al., 2016; Council, 2013; Gribble et al., 2013; Jansen et al., 2016).

Nutritional status is a major susceptibility factor for arsenic-related disease, at least in part through the impact of nutrition on one-carbon metabolism (OCM)(Council, 2013). OCM, a network of interrelated biochemical reactions dependent on sufficient intake of vitamin B_2 (riboflavin), vitamin B_6, folate (vitamin B_9) and vitamin B_{12}, plays an essential role in methylation processes throughout the body, including the methylation reactions involved in arsenic metabolism (Fig. 1)(Hall and Gamble, 2012; Howe et al., 2014). In studies from Bangladesh, both cross-sectional (Gamble et al., 2005) and folic acid supplementation trials demonstrated (Gamble et al., 2006; Peters et al., 2015) that higher folate is associated with increased arsenic methylation efficiency, resulting in higher DMA% and lower iAs% and MMA% in urine and in reduced blood arsenic concentrations. In cross-sectional studies, greater dietary intake of vitamins B_{12} and B_2 (Heck et al., 2007) and higher plasma B_{12} (Hall et al., 2009a) have been associated with lower iAs% and higher MMA%, in Bangladeshi adults. Further, both epidemiologic (Chung et al., 2006; Pilsner et al., 2009; Zablotska et al., 2008) and experimental studies (Acharyya et al., 2015; Bhattacharjee and Pal, 2013) have reported OCM nutrients to be associated with lower risk for arsenic-related disease.

The generalizability of the OCM findings in Bangladesh to US populations with low-moderate arsenic exposure and different dietary patterns is unclear. We evaluated the association of OCM nutrients with arsenic metabolism biomarkers in the Strong Heart Study (SHS), a population-based cohort study initiated to assess cardiovascular risk factors in American Indian adults residing in Arizona, Oklahoma and North and South Dakota. We used dietary intake estimates of B_2, B_6, folate and B_{12} as measures of OCM nutrients and percentages of urinary inorganic arsenic (iAs%) and its methylated metabolites (MMA% and DMA%), as measures of arsenic metabolism. We also modeled the complexity of both arsenic metabolism profiles and nutrition intake through the use of principal component analysis (PCA).

2. Methods

2.1. Study population

The SHS recruited 4549 American Indians from 13 tribes located in Arizona, Oklahoma and North and South Dakota. Eligible participants were men and women aged 45–74 years at the baseline visit in 1989–1991. The overall participation rate was 62%. All participants provided informed consent and study protocols were approved by multiple institutional review boards, community members and The Indian Health Service. In 2016, one of the communities withdrew their consent for participating in future studies, reducing the overall sample size to 3516. The final version of this manuscript, along with a lay summary, was sent to, and approved by, all remaining communities.

At the baseline visit (1989–1991), a random sample of 50 males and 50 females from each age decade and at each study site ($n = 722$; 508 after excluding the community that withdrew consent) was selected to participate in a self-administered food frequency questionnaire (FFQ), which provided estimated long-term daily average intake of folate and vitamins B_2, B_6 and B_{12}.(Committee, 1989) We excluded 94 participants with missing data on urine arsenic, and 9 participants missing data on education, alcohol intake, smoking status, body mass index (BMI), estimated glomerular filtration rate (eGFR), and urine creatinine, leaving 405 participants for this study. Participants included in this study were similar to the overall study population on most variables of interest, with the exception of being slightly older than the full cohort (Supplemental Material Table S1).

2.2. Data collection

Baseline visits included bio-specimen collection, a physical exam, and an interview-administered questionnaire. Visits were performed by trained and certified examiners according to a standardized protocol. Details have been described previously(Lee et al., 1990).

2.2.1. Urine arsenic metabolites

Morning spot urine samples were collected during baseline visit in polypropylene tubes, frozen within 1–2 h of collection, shipped buried in dry ice and stored at < -70 °C in the Penn Medical Laboratory, MedStar Research Institute, Washington, DC(Lee et al., 1990). The freezers have been operating under a strict quality control system to guarantee secure sample storage. For arsenic analyses, urine samples were thawed in 2009–2010, and up to