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Non-monotonic relationships between arsenic and selenium excretion and its implication on arsenic methylation pattern in a Bangladeshi population

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ABSTRACT

The toxicity of arsenic differs markedly between individuals and populations, which might be related to the metabolism (methylation) of inorganic arsenic (As), as well as the selenium (Se) nutritional status. Urinary excretion of As (u-As) and Se (u-Se) was examined in an adult population ($n=128$) living in an As-contaminated area in Bangladesh. Although there was a significant negative correlation between u-Se and u-As (median 137; range 49–927 μg/g creatinine), closer examination revealed a non-monotonous relationship between them. A quadratic curve with an axis of As at 155 μg/g Cre gave a better fit, and u-As and u-Se were positively or negatively correlated depending on whether the As concentration was lower or higher than 155 μg As/g Cre, respectively. Likewise, the relationships between the As methylation pattern and glutathione-S-transferase (GST) polymorphism, body mass index (BMI), and u-Se differed depending on the u-As range; i.e., higher or lower than 155 μg/g Cre. Although we did not determine the causal mechanism for these observations, the non-monotonic relationship between As exposure and the variables examined suggested the existence of a threshold at which the handling of As by human body is qualitatively changed. The possible importance of Se nutrition for As toxicity is also discussed.

1. Introduction

The contamination of ground water by arsenic (As) has been observed in many Asian and Latin American countries. Exposure to inorganic arsenic (iAs) from drinking water has been associated with cancers of the skin and internal organs (including the bladder and lungs), diabetes, hypertension, and neonatal development (NRC, 2001), generating major public health concerns worldwide. Bangladesh has been confronted with severe As groundwater contamination problems because the vast majority of Bangladeshi people use tube wells to obtain water for drinking and cooking on a daily basis. The population at risk, as defined by use of tube wells where water exceeds the Bangladesh standard of 50 μg As/L, is estimated to be around 50 million (Bae, 2003). This number is much larger if the WHO-recommended value of 10 μg As/L, adopted by many developed countries, is considered.

A distinctive feature of As toxicity is its remarkable inter-individual and inter-population variability (Chen et al., 2003; Mead, 2005), which is at least partly due to the fact that inorganic As undergoes metabolism after ingestion. The process is influenced by a variety of factors, resulting in several metabolites with varying toxicity. Thus, the modification of As toxicity by age (Bae, 2003; Guifan Sun et al., 2007), sex (Watanabe et al., 2001; Rahman et al., 2006), pregnancy (Concha et al., 1998) as well as dietary (Maharjan et al., 2007) and genetic (Engström et al., 2007; Lin et al., 2007; Steinmaus et al., 2007; Li et al., 2008; Agusa et al., 2010) factors has been reported in human populations and in many experimental studies.

Among the dietary factors, Se is one of the most extensively examined nutrients in relation to As toxicity and metabolism. However, the reported findings are mixed. One line of evidence suggests that Se has a protective effect against As toxicity in terms

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of the motor function of children (Parvez et al., 2011) and the prevention of skin lesions (Lin et al., 2007), while As and Se both exert global hypomethylation of genomic DNA, a mechanism considered to contribute to As toxicity (Pilsner et al., 2011). Se and As are thought to kinetically interact with each other, although the nature and mechanism of the interaction have not been determined (Wu et al., 2001). For example, the urinary excretion of these metals have been reported to have a negative correlation in Bangladesh (Miyazaki et al., 2003) and a positive correlation in Taiwan (Chen et al., 2003) and in Chile (Christiana et al., 2006). In plasma, there is a negative correlation between Se and As, and the methylation of As is affected by Se (Pilsner et al., 2011), although some studies have not observed this relationship (Lindberg et al., 2008). It should be noted that in the urinary excretion studies mentioned above, the Bangladeshi population had a much higher level of As exposure than the other two populations (Hsueh et al., 2003; Miyazaki et al., 2003; Christiana et al., 2006), suggesting that the differences observed might be due to a difference in the exposure levels.

With regard to the genetic factors, various genetic polymorphisms that can modify As metabolism and/or toxicity have been proposed, including, arsenic (III) methyltransferase (AS3MT) (Engström et al., 2007; Lin et al., 2007), isozymes of glutathione-S-transferases (GSTs), and purine nucleoside phosphorylase (PNP) (Watanabe, 2012). GSTs comprise a large family of ubiquitous and multifunctional enzymes, of which GSTO1 has been shown to reduce pentavalent As(V) to the trivalent form (Zakharyan et al., 2001) using glutathione (GSH). GSTT1 and GSTM1 are members of the GST family, with both having deletion polymorphisms that are devoid of enzyme activities (Pemble et al., 1994; Xu et al., 1998). Unlike with GSTO1, the role of these isozymes in As metabolism has not been confirmed, but the deletion of either of them is associated with an increased risk of cancers (Hayes and Strange, 2000). Furthermore, some polymorphisms in these enzymes have been associated with As metabolism/toxicity, although the results are somewhat mixed (Chiou, 1997; Engström et al., 2007; Lin et al., 2007; Steinmaus et al., 2007).

Most of the studies on the genetic effects are conducted at relatively lower exposure levels, and the studies conducted in Bangladesh and West Bengal in India, with very high exposure levels (Ghosh, 2006; McCarty et al., 2007b), did not examine the As metabolism in relation to the polymorphisms.

These mixed observations led us to hypothesize that the relationship between As metabolism/ toxicity and potential confounders is As-dose dependent. A recent theoretical study using simulation model of As metabolism indicated that the major determinants of As metabolism in hepatocytes can differ substantially according to As exposure level (Stamatelos et al., 2011). To clarify the practical relevance of such theoretical findings, this study examined two modifying factors (Se and genetic polymorphisms) in terms of their effects on As metabolism, together with several other factors known to influence As metabolism. We selected a population in Bangladesh with a wide within-population range of exposure to As through the consumption of groundwater. For genetic polymorphisms, we focused on the effect of GSTT1 or GSTM1 deletion, which are found with a relatively high frequency in this population and might be associated with As metabolism.

2. Subjects and methods

2.1. Study area and population

The study areas were two rural communities, i.e., Sherpur Vandar and Sadashibpur in Nawabganj district, northwestern Bangladesh, located around 5 km from each other. The environmental setting and subsistence of the both communities were similar to each other; both communities were located in a plain area, mostly covered by paddy field and crop lands, having no major upland areas, and therefore sharing common weather/climatic patterns. Approximately 50% of the residents in both communities were engaged in farming, cultivating rice, jute, vegetables, and mango and additional 25–30% were engaged in small-scale retailing. The structure of houses and their variation as well as possession of the livestocks and other assets were also similar. The inhabitants relied on groundwater for drinking and cooking on a daily basis. The tube wells they used provided water contaminated by arsenic, with a concentration varying from less than 10 to more than 500 μg/L (Watanabe, 2001, 2004).

The study was supported by the Ministry of Environment and Ministry of Education, Culture, Sports, Science, and Technology, Japan. The study protocol was approved by the Research Ethics Committee at Graduate School of Medicine in the University of Tokyo (approval number 1948) and by the Ethical Review Committee of the National Institute of Preventive and Social Medicine (NIPSOM) in Dhaka, Bangladesh.

2.2. Sample collection and interviews

The field survey was conducted by a team of Bangladeshi and Japanese researchers in September 2007. In each community, a health station was established, and local staffs made door-to-door visit to invite residents to voluntary participate in the survey. Before participation, the local staff explained to the potential participants the purpose and the protocol of the survey, and obtained written consent. In response to the invitation, 128 adults (68 males and 60 females, 18–58 years old) participated in the study. At the health station, well-trained Bangladeshi staff interviewed participants to obtain basic demographic information. Blood samples were collected by Bangladeshi nurse in a tube containing EDTA, and all samples were immediately centrifuged to separate blood cell and plasma. Urine samples were collected in polypropylene tubes. Samples were kept in cooler box with dry ice and later transported to the University of Tokyo, Japan, where they were stored at −80 °C until analyses.

2.3. Chemicals

Sodium arsenite ($NaAsO_2$), sodium arsenate ($Na_2HAsO4Na \cdot 7H_2O$), and monomethyl arsonic acid ($(CH_3)AsO(OH)_2$) were purchased from Wako Pure Chemical Industries Ltd., Japan., Dimethylarsenic acid ($(CH_3)2AsO(OH)$) from Tri Chemicals Co. Ltd., Japan. Stock solutions for all As compounds were prepared at a concentration of 1000 μg As/L, and kept at −80 °C. Working solutions at concentration of 10 μg As/L were prepared daily from the stock solutions.

2.4. As and Se measurement and chemical speciation of As in urine

Urinary total As (u-As) and Se (u-Se) were determined by inductively-coupled plasma mass spectrometry (ICP-MS: Agilent 7500ce, Agilent technologies Japan, Tokyo, Japan) using the helium gas mode. The urine samples were diluted 20-fold with MilliQ water containing 1% nitric acid and 2% buthanol before measurement. Speciation analysis was performed by HPLC coupled with ICP-MS (HPLC-ICP-MS). For the HPLC system, JASCO Gulliver Series (PU-980) equipped with a polymer-based anion exchange column (Gelpack GL-IC-A15, 150 mm × 4.6 mm i.d., Hitachi-kasei, Japan) was used. Mobile phase was 0.2 mM EDTA–2Na/2.0 mM phosphate buffer, pH 6.0. Four peaks identified as As (III), As (V), monomethyl-arsonic acid (MMA), and dimethylarsinic acid (DMA)