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Joint effects of urinary arsenic methylation capacity with potential modifiers on arsenicosis: A cross-sectional study from an endemic arsenism area in Huhhot Basin, northern China ☆

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ABSTRACT

A lower arsenic methylation capacity is believed to be associated with various arsenic-related diseases. However, the synergistic effect of the arsenic methylation capacity and potential modifiers on arsenicosis risk is unclear. The current study evaluated the joint effect of the arsenic methylation capacity with several risk factors on the risk of arsenicosis characterized by skin lesions. In total, 302 adults (79 arsenicosis and 223 non-arsenicosis) residing in an endemic arsenism area in Huhhot Basin were included. Urinary levels of inorganic arsenic (iAs), monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) were determined, and the percentages of arsenic species (iAs%, MMA%, and DMA%), as well as two methylation indices (primary methylation index, PMI, and secondary methylation index, SMI), were calculated to assess the arsenic methylation capacity of individuals. The results showed that a lower methylation capacity, which is indicated by higher MMA% values and lower DMA% and SMI values, was significantly associated with arsenicosis after the adjustment for multiple confounders. The relative excess risk for interactions between higher MMA% values and older age was 2.35 (95% CI: −0.56, 5.27), and the relative excess risk for interactions between higher MMA% values and lower BMI was 1.08 (95% CI: −1.20, 3.36). The data also indicated a suggestive synergistic effect of a lower arsenic methylation capacity (lower DMA% and SMI) with older age, lower BMI, and male gender. The findings of the present study suggest that a lower arsenic methylation capacity was associated with arsenicosis and that certain risk factors may enhance the risk of arsenic-induced skin lesions.

1. Introduction

Chronic arsenic poisoning is a major public health problem in many countries around the world, and an estimated 130 million people consume arsenic-contaminated drinking water worldwide (Marchiset-Ferlay et al., 2012). A recent study emphasized that 19.6 million people may face arsenic poisoning throughout China (Rodriguez-Lado et al., 2013). Epidemiologic studies have shown that the chronic ingestion of arsenic in drinking water is associated with various skin lesions (Seow et al., 2012), hypertension (Abhyankar et al., 2012), cardiovascular diseases (Balakumar and Kaur, 2009), metabolic syndrome (Wang et al., 2007), and diabetes (Pan et al., 2013), as well as cancers of the skin, lung, liver, and bladder (Bhattacharjee et al., 2013). In general, the appearance of skin lesions, which include pigmentation and/or depigmentation on the trunk and hyperkerotosis on the palms and on the soles (Sun, 2004), is the first visible and most prominent symptom of chronic arsenic exposure. Studies indicate that the appearance of skin lesions is associated with arsenic-induced basal and squamous cell skin cancers (Chen et al., 2006). Therefore, premalignant skin lesions are considered precursors of skin cancers, and the prevention of these lesions is a critical public health issue. Although the mechanism of arsenic-induced adverse health effects has not been fully understood, some studies suggest that arsenic metabolism is associated with arsenic-related diseases (Lindberg et al., 2008a, 2008b; Agusa et al., 2011; Li et al., 2013).

Abbreviations: iAs, inorganic arsenic; MMA, monomethylarsonic acid; DMA, dimethylarsinic acid; TMA, trimethylarsonic acid; tAs, total arsenic; PMI, primary methylation index; SMI, secondary methylation index; BMI, body mass index

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The arsenic is present in drinking water as inorganic arsenic (iAs). Inorganic arsenic can be rapidly and extensively absorbed by the gastrointestinal tract. It is generally accepted that iAs is primarily metabolized in liver, which is characterized by two steps of methylation (Vahter, 2002). Inorganic arsenic is first methylated to monomethylarsonic acid (MMA) and then to dimethylarsinic acid (DMA). This methylation facilitates the excretion of iAs from the body because the end products, MMA and DMA, are rapidly excreted in urine. In humans, iAs methylation is incomplete, and the composition of urinary arsenic metabolites varies from person to person in populations chronically exposed to arsenic from drinking water (Vahter, 1999). The percentage of urinary arsenic metabolites is usually used as an indicator for evaluating the methylation capacity of individuals, and two methylation indices, including PMI [(MMA+DMA)/tAs] and SMI [DMA/(MMA+DMA)], have also been applied to assess the arsenic methylation capacity in our previous studies (Sun et al., 2007; Xi et al., 2011).

Recent studies indicate that toxic intermediates are produced during arsenic metabolism (Le et al., 2000; Styblo et al., 2000). Cytotoxicity assays reveal that trivalent arsenic species are more toxic than pentavalent arsenic species and that MMA^{III} is the most toxic arsenic metabolite (Petrick et al., 2000). Previous studies suggested that a decreased arsenic methylation capacity, which is indicated by an increased MMA percentage (MMA%), a decreased DMA percentage (DMA%), or by a decreased SMI, is associated with several arsenic-induced diseases, including peripheral vascular disease, skin lesions, and bladder cancer (Tseng et al., 2005; Pilsner et al., 2009; Wu et al., 2013). In contrast, sex, age, nutrition, and genetic polymorphisms have been shown to explain the variation in the arsenic methylation capacity of humans (Lindberg et al., 2008b; Hall and Gamble, 2012; Engstrom et al., 2011; Chen et al., 2012). Studies in Bangladesh revealed a synergistic effect of arsenic exposure and the variables of sunlight exposure, smoking, and of fertilizer on the risk of arsenic-induced skin lesions (Chen et al., 2006; Melkonian et al., 2011). A recent study showed that the association between an incomplete arsenic methylation capacity and cardiovascular disease can be modified by older age and by cigarette smoking (Chen et al., 2013). However, few studies have focused on the synergistic effect of the arsenic methylation capacity and potential modifiers on the risk of arsenicosis characterized by skin lesions.

In this study, we analyzed arsenic metabolites in the urine of subjects with and without skin lesions among a higher arsenic-exposed population in rural China. We aimed to understand the association between the arsenic methylation capacity and arsenicosis and to understand the modification of the risk of arsenic-induced skin lesions by several potential risk factors.

2. Materials and methods

2.1. Study area and population

Inner Mongolia, with its capital established at Huhhot, is an autonomous region in northern China. This region was reported as an endemic arsenism area in 1989, and Huhhot Basin was one area with severe arsenicosis (Sun et al., 2011). This basin is an alluvial and lacustrine basin, which is in the region between the southern edge of the Da Qing Mountains and the northern bank of the Yellow River (Fig. 1). The center of the Huhhot Basin is the alluvial plain of the Da Hei River, where the groundwater is rich in naturally geogenic arsenic. The arsenic concentration in groundwater was reported to range from <1 to 1480 μg/L, and the rural population living in this area relies solely on groundwater for drinking and for domestic use (Smedley et al., 2003). Although a water supply improvement project has been progressively implemented in this area, some villages remain that use un-improved groundwater. Therefore, this study was performed in those villages whose water supply had not yet been improved.

According to the existing surveys of arsenic concentrations in drinking water by the local Centers for Disease Control and Prevention, two villages (V-1 and V-2) were involved in this study (Fig. 1). The distance between the two villages is 19 km, and the populations of the two villages are similar in lifestyles and in socioeconomic conditions. The villagers in this area engage in agricultural production and earn their money by selling farm products. The cross-sectional study was performed in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and was approved by the Ethics Committee of China Medical University. All villagers in the two villages were informed prior to participation in this study, and adult residents (above 18 years old) were included in the study based on the following requirements: (1) residents of Han nationality who lived in the same village for at least 10 years and (2) who had not ingested seafood in the past 7 days. Among 437 residents who were recruited for this study, 302 eligible subjects participated. Informed consent was read and signed by all of the participants before administering the questionnaire. Information concerning their demographic characteristics, socioeconomic status, lifestyle of smoking and drinking, dietary habits, medical history and others were obtained by well-trained interviewers according to the questionnaire. The measurements of standing height and body weight were completed by experienced physicians according to the standard methods.

2.2. Diagnosis of arsenicosis

Although chronic arsenic exposure can induce harmful effects on various organs in the human body, the resulting skin lesions are most prominent and easily distinguished clinical manifestations. Therefore, physical examinations with the emphasis on skin lesions induced by high arsenic exposure were performed by trained doctors according to the Diagnosis Standard on Endemic Arsenicosis of China (WS/T211-2001). Briefly, with high arsenic exposure, the grade of arsenicosis (suspicious, mild, moderate, and advanced) is determined by the degree of skin pigmentation, depigmentation, and hyperkerotosis on the palms of the hands and on the soles of the feet (Sun, 2004).

2.3. Arsenic in drinking water

The arsenic concentration in drinking water was estimated using the drinking water samples collected from the tube wells the participants used. Because a centralized tap-water system was established in village one (V-1) and supplied water to all villagers for daily life, only one drinking water sample was collected at the location of the water source in this village. For village two (V-2), there were eight tube wells. However, only five wells were used for the current daily water supply. Therefore, five drinking water samples were collected at the locations of the water sources in V-2. The determination of arsenic concentrations in water samples was performed using an atomic absorption spectrophotometer (AA-6800, Shimadzu Co. Kyoto, Japan) with an arsenic speciation pretreatment system (ASA-2sp, Shimadzu Co. Kyoto, Japan). The mean arsenic concentration of the 6 wells was 250 μg/L, with a range from 20 to 368 μg/L.

2.4. Urinary collection and measurement of arsenic metabolites

Spot urine samples (15 mL) were collected from all participants in polypropylene tubes and stored in an icebox. For each participant, 1 mL of urine was separately stored for creatinine (Cr) determination. Then, all the samples were transferred with dry ice to the Laboratory of Arsenic Analysis at China Medical University (Shenyang, China) and stored at -20 °C for further analysis.

Urinary arsenic metabolites, iAs, MMA, and DMA, were determined using an atomic absorption spectrophotometer (AA-6800, Shimadzu Co. Kyoto, Japan) with an arsenic speciation pretreatment system (ASA-2sp, Shimadzu Co. Kyoto, Japan). The arsenic speciation was based on the well-established hydride generation of volatile arsines, followed by cryogenic separation in liquid nitrogen. This method is credible and has been frequently used in our previous studies (Sun et al., 2007; Xu et al., 2008). Briefly, each urine sample was thawed at room temperature from -20 °C. In total, 1 mL of the sample was digested with 2N-NaOH solution at 100 °C for 3 h in a 15 mL polymethylpentene test tube, followed by stirring every 1 h. This digestion procedure has shown that iAs and methylated arsenic compounds do not undergo changes in chemical species. The absorbance of arsenic in the treated urine samples was determined at 193.7 nm. Quality control for arsenic determinations included the analysis of the Standard Reference Material of freeze-dried urine (SRM 2670, National Institute of Standards and Technology [NIST], Gaithersburg, MD, USA). The certified concentration value for arsenic was 480 ± 100 μg/L. The value determined in our laboratory was 474 ± 20 μg/L. The reliability of arsenic species separation was evaluated using the analytical recoveries of added arsenic species. Spiking urine samples with 10 μg/L of iAs, MMA, DMA and trimethylarsonic acid (TMA) resulted in recoveries of 81–92%, 88–98%, 89–103% and 80–95% for iAs, MMA, DMA and for TMA, respectively. Urinary Cr, which was used to account for urine dilution in spot urine samples, was determined using a Creatinine Assay Kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

2.5. Statistical analysis

The total arsenic (tAs) concentration in urine was defined as the sum of iAs, MMA, and DMA because no TMA was detected in any urine sample. The final reported urinary arsenic concentration was adjusted for urinary Cr by dividing the concentration of arsenic metabolites (μg/L) with Cr (g/L). Based on the concentrations of arsenic species, the percentages of urinary arsenic metabolites (iAs%, MMA% and DMA%) were defined