Toxicology and Applied Pharmacology 281 (2014) 11–18

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

Elevated levels of plasma uric acid and its relation to hypertension in arsenic-endemic human individuals in Bangladesh

Nazmul Huda [a,b,1], Shakhawoat Hossain [a,1], Mashiur Rahman [a], Md. Rezaul Karim [c], Khairul Islam [d], Abdullah Al Mamun [a], Md. Imam Hossain [a], Nayan Chandra Mohanto [a], Shahnur Alam [a], Sharmin Aktar [a], Afroza Arefin [a], Nurshad Ali [a], Kazi Abdus Salam [a], Abdul Aziz [a], Zahangir Alam Saud [a], Hideki Miyataka [e], Seiichiro Himeno [e], Khaled Hossain [a,*]

[a] Department of Biochemistry and Molecular Biology, Rajshahi University, Rajshahi 6205, Bangladesh
[b] Department of Medicine, Rajshahi Medical College, Rajshahi 6000, Bangladesh
[c] Department of Applied Nutrition and Food Technology, Islamic University, Kushtia 7003, Bangladesh
[d] Department of Biochemistry and Molecular Biology, Mawlana Bhashani Science and Technology University, Santosh, Tangail 1902, Bangladesh
[e] Laboratory of Molecular Nutrition and Toxicology, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan

ARTICLE INFO

Article history:
Received 23 June 2014
Revised 16 September 2014
Accepted 19 September 2014
Available online 2 October 2014

Keywords:
Arsenic
Bangladesh
Hypertension
Uric acid

ABSTRACT

Blood uric acid has been recognized as a putative marker for cardiovascular diseases (CVDs). CVDs are the major causes of arsenic-related morbidity and mortality. However, the association of arsenic exposure with plasma uric acid (PUA) levels in relation to CVDs has not yet been explored. This study for the first time demonstrated the associations of arsenic exposure with PUA levels and its relationship with hypertension. A total of 483 subjects, 322 from arsenic-endemic and 161 from non-endemic areas in Bangladesh were recruited as study subjects. Arsenic concentrations in the drinking water, hair and nails of the study subjects were measured by inductively coupled plasma mass spectroscopy. PUA levels were measured using a colorimetric method. We found that PUA levels were significantly ($p < 0.001$) higher in males and females living in arsenic-endemic areas than those in non-endemic area. Arsenic exposure (water, hair and nail arsenic) levels showed significant positive correlations with PUA levels. In multiple regression analyses, arsenic exposure levels were found to be the most significant contributors on PUA levels among the other variables that included age, body mass index, blood urea nitrogen, and smoking. There were dose–response relationships between arsenic exposure and PUA levels. Furthermore, diastolic and systolic blood pressure showed significant positive correlations with PUA levels. Finally, the average PUA levels were significantly higher in the hypertensive group than those in the normotensive group in both males and females living in arsenic-endemic areas. These results suggest that arsenic exposure-related elevation of PUA levels may be implicated in arsenic-induced CVDs.

Introduction

Arsenic is a potent environmental pollutant and human carcinogen that is ubiquitously present in food, soil, water and airborne particles. People are generally exposed to arsenic through contaminated drinking water, food, and air-dust. Occupational exposure to arsenic may also occur through the inhalation of arsenic dusts in the production and distribution processes. However, contaminated drinking water has been recognized as the major source of human exposure to arsenic (Ali et al., 2010; Smith et al., 2000). Arsenic poisoning is a global problem since arsenic contamination of ground water has been discovered in many countries including Bangladesh, India, Pakistan, Argentina, Mexico, Chile, United States of America, Taiwan and China. Arsenic poisoning has taken a serious turn affecting millions of people in Bangladesh (Smith et al., 2000). Elevated levels of arsenic have been reported in 61 out of 64 districts (administrative blocks) in the country and the scale of disaster has exceeded the Chernobyl catastrophe in Ukraine and Bhopal accident in India (Smith et al., 2000). Many people have died of the chronic diseases caused by prolonged exposure to arsenic. It has been assumed that 80–100 million people are at risk of arsenic poisoning in the country (Caldwell et al., 2003; Chowdhury, 2004; Chowdhury et al., 2000). Ingestion of inorganic arsenic has been documented to be associated with a variety of diseases including cancers, cardiovascular diseases (CVDs), dermatitis, neurotoxicity, diabetes

Abbreviations: BMI, Body Mass Index; BUN, Blood Urea Nitrogen; PUA, Plasma Uric Acid; CRM, Certified Reference Material; CRP, C-reactive Protein; CVDs, Cardiovascular Diseases; DBP, Diastolic Blood Pressure; ICAM-1, Intercellular Adhesion Molecule-1; LDL, Low Density Lipoprotein; Ox-LDL, Oxidized-LDL; SBP, Systolic Blood Pressure; VCAM-1, Vascular Cell Adhesion Molecule-1.

* Corresponding author. Fax: +880 721 750064.
E-mail address: khossainbio@gmail.com (K. Hossain).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.taap.2014.09.011
0041-008X/

mellitus, renal failure and liver dysfunction (Guha Mazumder et al., 1998; Islam et al., 2011; Karim et al., 2013; Meliker et al., 2007; Tapio and Grosche, 2006; Vahidnia et al., 2008; Wang et al., 2002).

Uric acid is the end product of purine metabolism in humans, and is excreted mainly in the urine. Hepatic production and renal and gut excretion of this compound occur through complex processes. The endogenous production of uric acid occurs in the liver, intestine, muscles, kidneys and the vascular endothelium. Many enzymes are involved in the conversion of two purine bases in nucleic acid, adenine and guanine to uric acid. The final reactions of uric acid production are the conversion of hypoxanthine to xanthine and then to uric acid by the enzyme xanthine oxidase. Humans cannot oxidize uric acid to the more soluble compound allantoine due to the lack of the enzyme uricase, as is different from the other mammals. Because of the functional mutations during the early stage of hominoid evolution, humans and other primates have no functional uricase, which leads to higher blood uric acid levels when compared to rodents. The plasma uric acid (PUA) levels are varied by multiple factors including environmental and genetic factors (Nath et al., 2007). The elevated level of blood uric acid is associated with gout. Pathologically, the increased levels of PUA lead to the formation of crystal deposits in joints, tendons and other tissues (Becker and Roessler, 1995). Besides the role of uric acid in the development of pathologic gout, however, a growing body of evidence has suggested that hyperuricemia is associated with the risk of CVDs including hypertension, metabolic syndrome, coronary artery disease, vascular dementia, stroke, preeclampsia, and kidney diseases (Cannon et al., 1966; Ford et al., 2007; Lehto et al., 1998; Roberts et al., 2005; Schretlen et al., 2007; Siu et al., 2006; Tuttle et al., 2001). Niskanen et al. (2004) conducted a prospective cohort study and showed that hypeuricemia is an independent risk factor for CVDs in middle-aged men. Furthermore, Storhaug et al. (2013) stated that serum uric acid is an independent marker of ischemic stroke in men, and the all-cause mortality in general Caucasian populations.

Many studies conducted in the arsenic-endemic populations in the world have clearly suggested that arsenic exposure is associated with CVDs (Chen et al., 2011; Karim et al., 2013; Wang et al., 2002). CVDs are the major causes of arsenic-related morbidity and mortality (Chen et al., 2011). Previously we and other groups have showed that arsenic exposure is associated with hypertension, a common form of CVDs (Hossain et al., 2012; Rahman et al., 1999). Although PUA is a putative marker for CVDs, the association between environmental arsenic exposure and PUA levels has not yet been documented. Therefore, the present study has been conducted to assess the relationship of chronic human exposure to arsenic with PUA levels especially in connection with hypertension.

Methods

Study areas and subjects. Ethical permission was taken from the Institute of Biological Sciences, University of Rajshahi, Bangladesh (21/320-IAMEBBC/IBSc). The subjects who participated in this study gave their written consent and all sorts of confidentialities and rights of the study subjects were strictly maintained. Arsenic-endemic and non-endemic study areas for this study were selected as described previously (Ali et al., 2010; Hossain et al., 2012; Islam et al., 2011; Karim et al., 2010). Arsenic-endemic areas were selected from the North-West region of Bangladesh that included Marua in Jessore, Dutpatila, Jajri, Vultie and Kestopur in Chuadanga, and Bheramara in Kushtia district of Bangladesh, and Chowkoli, a village in Naogaon district with no history of arsenic contamination was selected as a non-endemic area. Local residents (15–60 years of ages) who had lived for at least five years in arsenic-endemic and non-endemic areas were recruited for this study.

During the sample collection process, we were blinded to arsenic levels in the drinking water, hair and nails of the study participants. Attempt was made to match, as much as possible the following: age, sex and socioeconomic parameters (occupation, monthly income and education) of arsenic-endemic and non-endemic study subjects. The ratio of endemic to non-endemic subjects was approximately 2:1, and the ratio of male to female was approximately 1:1.

Pregnant and lactating mothers and the individuals who had a history of surgical operation, drug addiction, hepatitis B positive, hepatotoxic and anti-hypertensive drugs, malaria, kalazar, chronic alcoholism, history of hepatic, renal or severe cardiac diseases, and gout have been excluded from this study. Of the 331 individuals who were approached, 9 were excluded according to the exclusion criteria [i.e., study candidates ($n = 4$) who had lived in arsenic-endemic areas for less than 5 years, pregnant and lactating mothers ($n = 3$) and had hepatic diseases ($n = 2$)]; thus a total 322 were finally recruited in arsenic-endemic areas. In non-endemic area 4 [i.e., study candidates ($n = 2$) who had lived in the non-endemic area for less than 5 years, pregnant mother ($n = 1$), study subjects who underwent recent surgical operation ($n = 1$)] from 165 were excluded. The final participants in the non-endemic area were 161.

Household visits were carried out to interview residents. The personal interviews of the study subjects were carried out by the trained members of our research team using a standardized questionnaire. The information obtained from the interview included the sources of water for drinking and daily household uses, water consumption history, socioeconomic status, occupation, food habit, general food items consumed daily, cigarette smoking, alcohol intake, personal and family medical history, history of diseases, physiological complications, major diseases, previous physician's reports, and body mass index (BMI). We collected the blood and other specimens, and water samples on the same day at each site.

Blood pressure measurement. The standard protocol for measuring blood pressure recommended by World Health Organization (WHO) was used in this study. After the study subjects had rested for 20 min or longer, both systolic blood pressure and diastolic blood pressure (SBP and DBP) were measured three times with a mercury sphygmomanometer with subjects sitting. SBP and DBP were defined at the first phase and fifth phase Korotkoff sounds, respectively. The average of three measurements was used for the analysis. Hypertension was defined as a SBP of $\geq$140 mm Hg and a DBP of $\geq$90 mm Hg on three repeated measurements.

Water collection and arsenic analysis. Water samples used as primary sources of drinking water were collected for this study as described by Ali et al. (2010). Water samples from tube wells were collected in acid-washed containers after the well was pumped for 5 min as previously described (Van Geen et al., 2002). Total arsenic concentrations in water samples were determined by inductively coupled plasma mass spectroscopy (ICP-MS), (HP-4500, Agilent Technologies, Kanagawa, Japan) after the addition of a solution of yttrium (10 μg/L in 1.0% nitric acid) as an internal standard for ICP-MS analysis. All samples were determined in triplicate and the average values were used for data analysis. Accuracy of water arsenic measurement was verified using a certified reference material (CRM). "River water" (NMIJ CRM 7202-a No.347 National Institute of Advanced Industrial Science and Technology, Japan) was used as a CRM. The average value (mean $\pm$ SD) of arsenic in the "river water" determined in triplicate by ICP-MS was 1.06 $\pm$ 0.04 μg/L (reference value, 1.18 μg/L).

Collection of hair and nail samples, and analysis of arsenic. Arsenic levels in nails and hair have been reported to provide the integrated measures for arsenic exposure (Agahian et al., 1990; Gault et al., 2008). Hair and nails of the study subjects were collected and washed by the method as described previously (Ali et al., 2010). The washed samples were allowed to dry at 60 °C overnight and digested with concentrated nitric acid using a hot plate at 70 °C for 15 min and 115 °C for 15 min. After cooling, the samples were diluted with 1.0% nitric acid containing yttrium (10 μg/L). The concentrations of arsenic and yttrium