Chronic arsenic exposure, endothelial dysfunction and risk of cardiovascular diseases

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ABSTRACT: Cardiovascular diseases (CVDs) are the major causes of arsenic-related morbidity and mortality. Hypertension is a major risk of CVDs. Atherosclerosis is the main biochemical event of all forms of CVDs including hypertension. Atherosclerosis is a complex biochemical process in which several molecules are involved. However, underlying mechanism of arsenic exposure-related atherosclerosis leading CVDs especially hypertension has not yet been clearly understood. In our research, we have focused on the pathophysiology of arsenic-induced atherosclerosis leading to CVDs recruiting human subjects from arsenic-endemic and non-endemic rural areas in Bangladesh. We found that arsenic exposure metrics were positively associated with the elevated levels of diastolic (DBP) and systolic blood pressure (SBP) of the study subjects. We have also analyzed several circulating molecules related to vascular endothelial dysfunction and atherosclerosis including vasoconstrictors, and inflammatory, oxidative and adhesion molecules. We have demonstrated the relationship of arsenic exposure with these molecules. Our results suggest that exposure to arsenic is associated endothelial dysfunction probably through its pro-oxidative and pro-inflammatory properties. Our results also suggest that chronic exposure to arsenic impairs the vascular homeostasis leading to the development of hypertension and other forms CVDs. Thus, endothelial dysfunction and related biochemical events are the hallmarks of arsenic-induced cardiovascular diseases.

1 INTRODUCTION

Exposure to arsenic through drinking water is a major threat to the public health in many countries especially Bangladesh. Consumption of arsenic-contaminated water has turned into an environmental tragedy causing thousands of deaths in Bangladesh. Approximately 80–100 million people are at risk of arsenic toxicity in the country because of the consumption of higher concentrations of arsenic through drinking water than the permissive limit ($>10\text{ }\mu\text{g L}^{-1}$) set by World Health Organization (WHO). Chronic exposure to arsenic has been associated with CVDs (Huda *et al.*, 2014; Karim *et al.*, 2013; Rahman *et al.*, 1999). Hypertension is a risk of CVDs. However, mechanism of arsenic exposure-related CVDs especially hypertension has not yet been clearly understood. We therefore, explored the underlying mechanism of arsenic-induced CVDs especially hypertension recruiting human subjects from arsenic-endemic and non-endemic rural areas in Bangladesh.

2 METHODS

Study areas and study subjects were selected from the several villages in Bangladesh as we described previously (Ali *et al.*, 2010; Islam *et al.*, 2011, 2015; Karim *et al.*, 2010, 2013; Rahman *et al.*, 2015). Arsenic in the subjects' drinking water, hair and nails

were determined by inductively coupled plasma mass spectroscopy (ICP-MS). Circulating molecules were analyzed by bioanalyzer or microplate reader through commercially available kits. The standard protocol recommended by WHO was used for the measurement of blood pressure. Hypertension was defined as an SBP of $\geq 140\text{ mmHg}$ and a DBP of $\geq 90\text{ mmHg}$ on three repeated measurements. Statistical analysis for this study was done with Statistical Package for the Social Sciences (SPSS version 17.0).

3 RESULTS AND DISCUSSION

We found that subjects' drinking water, hair and nail arsenic concentrations were positively and significantly associated with DBP and SBP (Table 1) which indicated that chronic exposure to arsenic was associated with the elevation of blood pressure leading to hypertension. Endothelial function plays an inevitable role in vascular homeostasis. Endothelial dysfunction or damage is the major physiopathological mechanism implicated in the development of CVDs including hypertension. The presence of endothelial dysfunction is considered as clinical syndrome that is associated with and predicts an increased risk of CVDs (McLenachan *et al.*, 1990). Thrombomodulin (TM) is widely distributed on endothelial cell surface of the blood vessels as a high affinity receptor for thrombin. Soluble TM (sTM), a proteolytically cleavage form of

Table 1. Correlation of arsenic exposure metrics with subjects DBP and SBP levels.

Variables	Water As	Hair As	Nail As
DBP	$r_s = 0.332^*$	$r_s = 0.320^*$	$r_s = 0.293^*$
SBP	$r_s = 0.289^*$	$r_s = 0.279^*$	$r_s = 0.247^*$

As = Arsenic; * $p < 0.001$. No. of study subjects for DBP and SBP were 321.

thrombomodulin (TM) in blood represents the degree of endothelial damage. In our study (Hassibuzzaman *et al.*, 2017), we found that subjects' drinking water, hair and nails arsenic concentrations were positively associated with serum sTM levels. Previously, we also reported that arsenic exposure metrics were positively associated with the levels of plasma big endothelin-1 (Big ET-1) (Hossain *et al.*, 2012). Big ET-1 is a precursor form of well-known vasoconstrictor endothelin-1 (ET-1) and a marker of endothelial dysfunction. Positive association of arsenic exposure metrics with sTM and BigET-1 levels clearly indicate that chronic exposure to arsenic causes endothelial dysfunction. We also found that the hypertensive patients had significantly higher levels of sTM and Big ET-1 than the normotensive counterpart. Another important circulating molecule related to blood pressure or hypertension is angiotension II. Angiotension II, an important component of rennin-angiotensin system has strong vasoconstrictive activity. It can also increase the aldosterone level that acts on kidney tubule to reabsorb sodium and water. Reabsorption of sodium and water ultimately increases the blood volume causing elevation of blood pressure. Angiotensin II is produced from angiotensin I by angiotensin converting enzyme (ACE). Intriguingly, in our preliminary experiment, we found that arsenic exposure metrics were positively associated with circulating ACE levels. Positive association between arsenic exposure and ACE indicates that chronic exposure to arsenic causes dysfunction of rennin-angiotensin system. Our preliminary results also indicate that like sTM and Big ET-1, the study subjects who were hypertensive had a significantly higher level of ACE than the normotensive subjects. Our previous studies (Huda *et al.*, 2014; Karim *et al.*, 2013) demonstrated that chronic arsenic exposure metrics were positively associated with circulating inflammatory molecules (C-reactive protein and uric acid), adhesion molecules (intercellular adhesion molecule-1 and vascular cell adhesion molecule-1), and inversely associated with anti-inflammatory and anti-oxidative molecule (high density lipoprotein cholesterol-C). Increased levels of pro-inflammatory, pro-oxidative and adhesion molecules, and decreased levels of anti-inflammatory molecules have been reported to be implicated in the development of atherosclerosis leading CVDs through endothelial dysfunction. Arsenic exposure-related endothelial dysfunction and elevated levels of vasoconstrictors and proatherogenic molecules may be the important features of arsenic-induced CVDs and hypertension.

4 CONCLUSIONS

Our results demonstrated that chronic exposure to arsenic was positively associated DBP and SBP. Associations of arsenic exposure with several circulating proatherogenic molecules indicate that chronic exposure to arsenic causes vascular endothelial dysfunction. Our results also suggest that arsenic exposure shift the vascular microenvironment toward vasoconstriction by increasing circulating vasoconstrictors. Taken together, our results reveal that endothelial dysfunctions and constriction of vascular system are the hallmarks of arsenic-induced CVDs especially hypertension.

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