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Arsenic exposures alter clinical indicators of anemia in a male population of smokers and non-smokers in Bangladesh

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ABSTRACT

Drinking water arsenic (WAs) exposure has been linked to a number of detrimental health outcomes including anemia, primarily among pregnant women. Little is known about the effects of arsenic (As) on hematological disorders among men. We have examined the role of As exposure on hematological indicators of anemia in a group of men exposed to a wide range of As in their drinking water. We conducted a cross-sectional investigation among 119 healthy men in the Health Effects of As Longitudinal Study (HEALS) cohort, in rural Bangladesh. The participants are part of an ongoing study focused on evaluating the influence of As and smoking on immune function. Samples were collected at recruitment and analyzed for water As, urinary As (UAs) and UAs metabolites to assess As exposure. Blood samples were also collected at recruitment and assayed immediately for hematological parameters. We found that increased WAs levels were associated with decreased red blood cell counts [$\beta = -0.13$, $p < 0.0001$] as well as hematocrit packed cell volumes [$\beta = -0.68$, $p = 0.008$] following adjustment for age, smoking, body mass index and polycyclic aromatic hydrocarbon-DNA adducts. Other measures of As exposure (UAs and its metabolites) demonstrated similar associations. Slightly stronger effects were observed among smokers. We also observed an effect of As on hemoglobin among smokers in relation to UAs [$\beta = -0.54$, $p < 0.05$]. Our analysis revealed effects of As exposure on hematological indicators of anemia in a group of healthy male smokers and non-smokers.

1. Introduction

As contamination in drinking water is a global public health problem affecting millions of people worldwide. The major arsenicals found in drinking water are the pentavalent and trivalent inorganic forms arsenate (As^{+5}) and arsenite (As^{+3}), respectively (Styblo et al., 2000; Naujokas et al., 2013). As a result, exposure to these inorganic arsenicals is of particular concern from a public health standpoint (Styblo et al., 2000). High-level As exposure has been linked with internal and external cancers, lung disease, immunosuppression, and cognitive impairment in children (Naujokas et al., 2013; Hughes, 2002; Tyler and Allan, 2014; Ferrario et al., 2016). A few studies have also indicated an association between chronic As exposure and hematological disorders such as anemia, particularly among women during pregnancy (Hopenhayn et al., 2006; Heck et al., 2008; Surdu et al., 2015; Kile et al., 2016).

Anemia is characterized by reduced red blood cell counts (RBC) and decreased hemoglobin (Hgb) levels in the blood. Anemia has been linked with a number of deleterious health effects, including fatigue, increased susceptibility to infection, cognitive and motor impairments, low birth weights, and risk of maternal and neonatal mortality (Balarajan et al., 2011; World Health Organization, WHO, 2011). A cross-sectional study of 217 Romanian women, found higher prevalence of anemia [prevalence proportion ratio (PPR) = 1.71, 95% (CI) 0.75–3.88], and particularly anemia during pregnancy [(PPR) = 2.87, 95% (CI) 0.62–13.26] associated with As exposure (Surdu et al., 2015). Similarly, a follow-up study of 810 pregnant women from two Chilean cities observed increased incidences of anemia related to As exposure. This study also revealed increasing prevalence of anemia with the progression of pregnancy among As exposed as compared to unexposed women (49% versus 17%) (Hopenhayn et al., 2006).

We have reported that higher urinary As (>200 μg/L) was linked to low Hgb (<10 g/dL) among 1954 men and women in the HEALS cohort in Bangladesh (Heck et al., 2008). Two studies from Bangladesh also

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reported an association between Hgb and arsenical-induced skin lesions (Breton et al., 2006; Kile et al., 2016). In a group of 147 women, Kile et al. (2016) observed that low Hgb (<12 g/dL) significantly increased risk [(OR) = 3.32, 95% (CI) 1.29, 8.52] of As-related skin lesions among women with normal Hgb levels after adjusting for As levels in drinking water and other covariates. Interestingly, the relationship between Hgb and arsenical skin lesions was found to be gender specific in a case-control study of 900 individuals from the same area of Bangladesh. Hgb was significantly associated with skin lesions only among males with a 40% reduction in the odds of skin lesions for every 1 g/dL increase in Hgb (OR = 0.60; 95% CI, 0.49–0.73). However, no direct associations (n = 184) were observed between toenail As or UAs species and Hgb levels (Breton et al., 2006).

Although a link between smoking and anemia has yet to be established, multiple diseases caused by smoking can result in anemia (Leifert, 2008). Several studies have found that smoking results in red blood cell hemolysis, which may be a contributing factor to anemia development (Minamisawa et al., 1990; Masilamani et al., 2016). Conversely, smoking has also been reported to complicate the identification of anemia by increasing Hgb and hematocrit packed cell volume (HCT/PCV) (Sagone and Balcerzak, 1975; Nordenberg et al., 1990; Anandha et al., 2014). These studies highlight the equivocal nature of the relationship between smoking and anemia and emphasize the need for further investigations.

There is strong evidence supporting an association between drinking water As exposure and anemia among women; however, very few studies have evaluated these relationships in men. To our knowledge, no studies have been conducted to determine the effects of smoking on anemia in As exposed individuals. Taking this into consideration, the present study assessed the relationships between chronic drinking water As exposure and hematological indicators of anemia among healthy male non-smokers and smokers in the HEALS cohort who live in rural Bangladesh.

2. Methods

2.1. Study population

The study was implemented in the HEALS cohort, an ongoing population-based prospective cohort in Araihazar, Bangladesh, a rural subdistrict, near the capital Dhaka (Parvez et al., 2006). The HEALS cohort was established to investigate the health effects of inorganic As (InAs) exposure from drinking water (Ahsan et al., 2006; Parvez et al., 2006). Briefly, between October 2000 and May of 2002 a total of 11,746 married (to reduce loss to follow-up) men and women were recruited between the ages of 18 to 75 years from a well-defined 25-km^2 geographical area where they had been residing for at least 3 years. The cohort was expanded to include an additional 8287 participants using the same methodology between 2006 and 2008. Most recently an additional 15,000 participants were recruited to the HEALS cohort totaling slightly over 35,000 adults. Participants in the HEALS cohort underwent demographic and lifestyle data collection using standardized questionnaires. Information on As exposure is assembled by collecting water and urine samples at multiple time points. A detailed description of the study cohort has been previously published and described (Ahsan et al., 2006).

2.2. Recruitment procedure

We adopted a similar protocol for recruiting study participants based on our past procedures. The study protocol was approved by the Institutional Review Board of Columbia University and the Bangladesh Medical Research Council. Informed consent was obtained from all participants. The study team visited the potential study participants at their home, explained the study procedure, and ascertained their eligibility criteria using a structured questionnaire. A potential list of participants for this study was formed based on As exposure, age, and smoking status from the HEALS central database. Upon further examination of the potential participants list, a number of participants were deceased, migrated out of the study area, or were suffering from a serious illness. Some eligible participants could not participate because they had taken employment out of the study area and visit home infrequently (e.g., only during weekends). A large number of participants were not eligible to participate because they stopped drinking water from wells with As concentrations (>50 μg/L). Persons identified with illnesses related to immune function and/or taking any medication that might have an impact on immune function, including medications for cardiovascular disease or diabetes were not enrolled in the study. If the participant was eligible, willing, and consented, an appointment was made for them at the field clinic. Our field team was able to identify 317 eligible participants to recruit for this study, out of which 267 participants visited our study clinic and completed the study procedure. We obtained and analyzed hematology and As exposure data from 119 individuals.

2.3. Questionnaire data, clinical examination and anthropometric measurement

Following consent to participate in the study, baseline in-person interviews were performed by trained personnel with detailed questionnaires on lifestyle characteristics. Participants were asked to provide information on demographics, medical co-morbidities, and cigarette and betel-nut usage. Questions were also answered on socioeconomic status defined by television ownership, land ownership, years of education, and occupation. Anthropometric measurements including height, weight, and blood pressure were performed using standard techniques.

2.4. Sample collection, processing, and shipment

Information on drinking water was collected at the time of recruitment. If the study participants used the same water source since 2000 and it had been tested by Columbia University in the past, then the individuals were consented into the study. Following consent, trained physicians collected a 20 mL venous blood sample and 40 mL spot urine sample from each participant.

Blood samples were collected by venipuncture using a vein in the antecubital fossa into dipotassium EDTA or sodium heparin anticoagulant tubes. Blood samples in heparinized tubes were processed immediately to isolate peripheral blood mononuclear cells (PBMC) and blood collected in EDTA tubes was used for hematology. All hematological parameters were measured immediately at the Araihazar Laboratory, Columbia University As and Health Research in Bangladesh. All the biological samples were labeled with machine-readable barcodes to maintain privacy of study participants.

2.5. Automated complete blood count (CBC)

A CBC was performed using a MYTHIC 22, a fully automated (Microprocessor controlled) hematology analyzer used for the in vitro diagnostic testing of whole blood specimens. MYTHIC 22 is an optical measurement system for analyzing up to 22 hematological parameters.

2.6. Water sample collection and measurement of As

Procedures for field sample collection and laboratory analyses are described elsewhere in detail (Cheng et al., 2004; Van Geen et al., 2005, 2007). Water samples were analyzed by high-resolution inductively coupled plasma mass spectrometry (HR ICP-MS) as previously described (Van Geen et al., 2007). The analytical detection limit of the method is 0.1 μg/L; the standard deviation of a single measurement is conservatively estimated at 4 μg/L (Van Geen et al., 2005).