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Cross sectional association of arsenic and seroprevalence of hepatitis B infection in the United States (NHANES 2003–2014)

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ABSTRACT

Background: Arsenic alters immunological parameters including antibody formation and antigen-driven T-cell proliferation.
Objective: We evaluated the cross-sectional relationship between urinary arsenic and the seroprevalence of hepatitis B (HBV) infection in the United States using data from six pooled cycles of the National Health and Nutrition Examination Survey (2003–2014, N = 12,447).
Methods: Using serological data, participants were classified as susceptible, immune due to vaccination, or immune due to past natural infection. We used multinomial logistic regression to evaluate the association between urinary DMA and HBV classification. A sensitivity analysis using total urinary arsenic (TUA) was also conducted. Both DMA and TUA were adjusted for arsenobetaine using a residual regression method
Results: A 1-unit increase in the natural logarithm (ln) of DMA was associated with 40% greater adjusted odds of having immunity due to natural infection compared to being susceptible (Odds Ratio [aOR]: 1.40, 95% Confidence Intervals [CI] 1.15, 1.69), 65% greater odds of having immunity due to a natural infection (aOR: 1.65, 95% CI: 1.34, 2.04) and 18% greater odds of being susceptible (aOR: 1.18, 95% CI: 1.05, 1.33) compared to being immune due to vaccination after adjusting for creatinine, age, sex, race, income, country of birth, BMI, survey cycle, serum cotinine, recent seafood intake, and self-reported HBV immunization status.
Conclusion: In the U.S. general public, higher urinary arsenic levels were associated with a greater odds of having a serological classification consistent with a past natural hepatitis B infection after adjusting for other risk factors. Additionally, higher urinary arsenic levels were linked to a greater odds of not receiving hepatitis B vaccinations. Given the cross-sectional nature of this analysis, more research is needed to test the hypothesis that environmentally relevant exposure to arsenic modulates host susceptibility to hepatitis B virus.

1. Introduction

Chronic arsenic exposure is immunotoxic (Burchiel et al., 2009; Dangleben et al., 2013; Martin-Chouly et al., 2011; Soto-Peña et al., 2006). Considering that approximately 100 million people worldwide are chronically exposed to arsenic through their drinking water (Naujokas et al., 2013), it is important to examine the potential for arsenic to influence human susceptibility to infectious agents. *In vitro* studies using cell culture have reported that high doses of arsenic increase apoptotic rates in B-cells, T-cells, macrophages and neutrophils (Dangleben et al., 2013). Additionally, a well-designed in vivo study using mice demonstrated that environmentally-relevant inorganic arsenic exposure levels of 100 parts per billion of arsenite in drinking water enhanced the morbidity and mortality of H1N1 influenza (Kozul et al., 2009). Epidemiological studies also report that chronic arsenic exposure is associated with higher rates of infectious diseases including pneumonia, respiratory illnesses, and diarrheal disease (Argos et al., 2010; Parvez et al., 2010; Rahman et al., 2011; Raqib et al., 2009., George et al., 2015).

There is also growing evidence gathered from epidemiological studies that demonstrate that arsenic exposure is associated with antibodies against viral hepatitis. Viral hepatitis is a common infectious disease that inflames the liver, which is also a target organ for arsenic toxicity. There are at least five different types of viral hepatitis: A, B, C, D and E. Data from a large prospective birth cohort in Bangladesh showed that women with higher arsenic exposure had higher odds of hepatitis E virus seroconversion during pregnancy (Heaney et al., 2015). In the United States, a large cross-sectional study showed that arsenic exposure was associated with higher hepatitis A seroprevalence although we were unable to determine if arsenic exposure increased

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Table 1
Classification of hepatitis B viral status based on serological markers available in NHANES 2003–2014.

Serological marker	Abbreviation	Susceptible	Vaccinated	Natural Infection	Acute/Chronic HBV infection
Hep B Surface Antibody	Anti-HBs	-	+	+	-
Hep B Surface Antigen	HBsAg	-	-	-	+
Total Hep B Core Antibody	Anti-HBc	–	–	+	+
Sample size		8520	3491	436	33[a]
Weighted prevalence (95% CI)		71.9% (70.8 0–72.9)	25.0% (23.9–26.0)	3.1% (2.7–3.5)	–

[a] These individuals were excluded from the analysis due to insufficient power across covariates.

susceptibility to the virus (Cardenas et al., 2016). The hepatitis B Virus (HBV) is also a common hepatitis virus that is mainly transmitted through contact with infected blood, semen, or other bodily fluid (CDC, 2010a). A vaccine to prevent HBV infection was first developed in the 1980s and recommended for high risk populations including health care workers, sexually active individuals, men who have sex with men, individuals travelling to countries where hepatitis is common, and intravenous drug users (Mast et al., 2006; Weinbaum et al., 2008). As of 1991 the Centers for Disease Control and Prevention (CDC) recommends all newborns receive HBV vaccination with the final dose administered at 18 months of age. This prevention strategy has been highly effective and the incidence of hepatitis B has decreased dramatically (Smith et al., 2012). As of 2014, the CDC recorded 2953 new cases of acute hepatitis B in the United States although the actual number of new cases is estimated to be 6.48-times higher (CDC, 2010b).

While preventing contact with infected biological materials and vaccination are the most effective ways to reduce HBV transmission, identifying environmental factors that can affect HBV infection could inform novel prevention strategies, particularly in developing countries facing ubiquitous exposure to environmental toxicants and high prevalence rates for infectious diseases. Thus, the objective of this study was to investigate the association between arsenic exposure and HBV status as defined by serological markers in a large representative sample of the U.S. population. We hypothesized that higher urinary arsenic concentration would be associated with a higher prevalence of a natural HBV infection after controlling for other risk factors as potential confounders. We further hypothesized that only individuals with no doses of the hepatitis B vaccine would be at increased odds of infection with elevated arsenic exposure.

2. Methods

2.1. Study population

We used data from six consecutive cycles of the National Health and Nutrition Examination Survey (NHANES) which is representative of the U.S. civilian non-institutionalized population at midpoint between the 2003–2014. These cycles were selected because urinary arsenic measurements and serological markers for HBV were available in participants aged 6 years and older and collected consistently across all 6 cycles. Informed consent was obtained from all survey participants and study protocols were approved by the National Center for Health Statistics research ethics review board (CDC, 2012).

NHANES only performs urinary arsenic measurements in one third of participants aged 6 years and older (n = 15,663 in the six survey cycles). Of those participants, 14,285 also had complete data available on their HBV serology for classification and 12,492 with complete covariate information. To avoid potential confounding by immunodeficiency, we excluded participants with a positive or equivocal HIV test (n = 26), unclear classification of hepatitis B serology (n = 128) or with acute or chronic Hepatitis B infection (n = 33) leaving a total of N = 12,447 participants for this analysis.

2.2. Serological markers

At the time of examination, participants provided blood via venipuncture. Samples were processed by the Division of Viral Hepatitis. Hepatitis B surface antibody (anti-HBs) was qualitatively measured using a solid-phase competitive enzyme immunoassay (Ausab, Abbott Laboratories). A quantitative enzyme-linked immunoassay was used to measure the HBV core antibody, anti-HBc (Vitros, anti-HBc ELISA). If the sample tested positive for anti-HBc it was also tested for the hepatitis B surface antigen, HBsAg (Auszyme, Abbott Laboratories). If the sample tested negative for anti-HBc it was coded as negative for HBsAg. All serological markers are qualitatively reported as positive or negative by NHANES (CDC, 2014a, 2014b).

We used the clinical combination of HBV antibodies and the hepatitis B antigen (HBsAg) to determine three categorical classification for hepatitis B infection. If participants were coded negative for anti-HBs, anti-HBc and HBsAg they are considered susceptible to HBV (i.e. never infected or vaccinated). If participants were coded positive for both anti-HBs and anti-HBc but not HBsAg they were considered as having a past natural infection. Finally, if participants were coded positive for anti-HBs but negative for anti-HBc and HBsAg, they are considered to be immune due to vaccination (CDC, 2010b; Mast et al., 2005). Interpretation of the serological markers provided by the CDC are summarized in Table 1. We were unable to distinguish between acute or chronic HBV infection because the immunoglobulin M class of anti-HBc which becomes detectable at the onset of acute hepatitis B was not measured in NHANES. Therefore, we excluded 33 participants from this category and 128 with an unclear combination of hepatitis B serological markers that had complete exposure and covariate information.

2.3. Urinary arsenic assessment

Urine samples were analyzed within 3 weeks of collection using high performance liquid chromatography (HPLC) coupled to inductively coupled-plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS). This method quantifies total urinary arsenic and species from which we selected dimethylarsenic acid (DMA), arsenobetaine (AsB), and total urinary arsenic for analyses (Caldwell et al., 2008). The corresponding limits of detection (LODs) for total urinary arsenic were 0.6 μg/L (2003–2004), 0.74 μg/L (2005–2010), 1.25 μg/L (2011–2012) and 0.26 μg/L (2013–2014). The LOD for DMA and AsB were 1.7 μg/L and 0.4 μg/L, respectively for the 2003–2010 NHANES cycles. For the 2011–2012 NHANES cycle the LOD for DMA and AsB was 1.8 μg/L and 0.28 μg/ respectively. Finally, for the 2013–2014 NHANES cycle the LOD for DMA and AsB was 1.91 μg/L and 1.16 μg/L. The proportion of urine samples that were below the limit of detection (LOD) in our study for all the cycles was 1.31% for total urinary arsenic, 17.32% for DMA and 43.54% for AsB. Concentrations below the LOD are reported in NHANES as the LOD divided by the square root of two for each analyte.

AsB is found in seafood and considered to be relatively nontoxic (Choi et al., 2010; Heinrich-Ramm et al., 2002). Therefore, we uses a residual method to provide an estimate of arsenic exposure that minimizes the potential influence of seafood arsenic intake (Jones et al., 2016). This approach yields a calibrated urinary biomarker by regressing DMA by AsB and extracting the model residuals [e.g. $\ln(DMA_i)$