Arsenic exposure, lung function, vitamin D and immune modulation in the Health Effects of Arsenic Longitudinal Study (HEALS) cohort

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ABSTRACT: Epidemiologic research, including our own, has demonstrated associations of arsenic (As) exposure with impaired lung function. While an overwhelming number of recent reports demonstrates a protective role of vitamin D (vit. D) on the respiratory system, its role on lung function in an As exposed population has not been evaluated. In an ongoing study in the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh, we have observed a positive association between serum vit. D and lung function among people exposed to As. Our data show a strong adverse association between water As and lung function among individuals with low vit. D ($\leq 15 \text{ ng mL}^{-1}$). The findings suggest that people with adequate levels of vitamin D are less likely to experience impairment of lung function associated with As. Our research has important public health implications in As exposed populations around the globe.

1 INTRODUCTION

Chronic exposure to water arsenic (WAs) has been linked to non-malignant respiratory outcomes including respiratory symptoms, airway epithelial damage, impaired lung function, respiratory infections, prevalence and mortality from COPD. Impaired lung function has also been observed in populations exposed to As from Chile, India and Pakistan. In a longitudinal analysis, we have observed a significant decline of FEV1 (-80.6 mL , $p < 0.01$) and FVC (-97.3 mL , $p = 0.02$) in the study participants ($N = 950$) exposed to WAs $> 97 \mu\text{g L}^{-1}$ as compared to those exposed to $< 19 \mu\text{g L}^{-1}$. Notably emerging evidence suggests a protective effect of Vitamin D (vit. D) on lung function, however, a role of circulating vit. D on lung function in As exposed populations has not been evaluated.

We are conducting an epidemiological investigation to examine the effects of long term As exposure, at low-to-moderate levels, on lung function and immune function as well as a possible protective role of vit. D on As-related lung function in the Health Effects of Arsenic Longitudinal Study (HEALS) participants in Araihaazar, Bangladesh.

2 MATERIALS AND METHODS

The HEALS cohort was established in Araihaazar in 2000, Bangladesh, to prospectively examine health

effects of As exposure from drinking water among $\sim 35,000$ adults and their children. Since recruitment, we have been following HEALS participants for their health status using a number of procedures including active quarterly in person visits by research assistants, bi-annual visits by physicians, and regular surveillance by village health workers. During the follow-up visits all cohort members were evaluated by trained physicians using standard protocol to ascertain lung disorders.

For this analysis, we utilized preliminary findings from an ongoing investigation. The aims of the project are to evaluate effects of long terms exposure to As on lung function, immune function and serum vit. D in a group of adults ($N = 630$) in the HEALS cohort.

2.1 Assessment of exposure and study outcomes

Assessment of exposure: Water, urine and urinary As were measured by high-resolution inductively-coupled plasma mass spectrometry (HR-ICP-MS).

Assessment of study outcomes: We conducted pre- and post-bronchodilator administered *Lung function tests (PFT)* using a portable spirometer (Koko, nSpire Health, Longmont, CA) and were scored based on acceptability criteria developed according to ATS guidelines. We have included only post-bronchodilator PFT data for this analysis.

Vitamin D (25-hydroxyvitamin D2 and 25-hydroxyvitamin D3) were measured simultaneously in serum using Ultra-Performance Liquid Chromatography combined with tandem mass spectrometry (LC-MS/MS) following liquid-liquid extraction.

T-cell function was determined by activating T-cell with anti-CD3/anti-CD28 in peripheral blood mononuclear cell (PBMC) samples.

3 RESULTS AND DISCUSSION

We have conducted an interim analysis in 231 individuals to assess the relationship between As exposure and lung function, vit. D and immune function. At the Arsenic Conference in July we will present findings utilizing a larger dataset.

In the current analysis, we observe an inverse association between As exposure and lung function, particularly among smokers and males. Our analysis shows that WAs exposure was inversely associated with Forced Expiratory Volume in 1 sec (FEV₁) ($r = -0.20$, $p < 0.05$) and Forced Vital Capacity (FVC) ($r = -0.23$, $p = 0.02$) among smokers. The relationships among non-smokers were as follows: FEV₁ ($r = -0.15$, $p = 0.06$) and FVC ($r = -0.16$, $p = 0.04$). Among males we observed an association between WAs and lung function [FEV₁ ($r = -0.16$, $p = 0.09$) and FVC ($r = -0.19$, $p = 0.04$)]. Similar relationships were also observed with urinary As (UAs).

We have found a positive association between vit. D and FEV₁ ($r = 0.22$, $p < 0.01$) and FVC ($r = 0.23$, $p < 0.01$). In contrast, WAs ($r = -0.15$, $p = 0.09$) and UAs ($r = -0.38$, $p = 0.006$) were found to significantly inhibit serum vit. D. Importantly, our data show a strong negative association between WAs and FEV₁ ($r = -0.46$, $p = 0.09$) and FVC ($r = -0.54$, $p = 0.04$) and FVC among individuals with low serum vit. D (≤ 15 ng/ml) as compared to those with high vit. D level (> 15 ng/ml) for FEV₁ ($r = -0.13$, $p = 0.18$) and FVC ($r = -0.05$, $p = 0.57$).

Additionally, we have observed that a number of cytokines (IL-4, IL-8, IL-10, IL-17 α , IL-1 β and TNF α) were significantly inhibited by WAs. IL-17 α was one of the most affected cytokines by WAs ($r = -0.40$, $p < 0.07$) and UAs ($r = -0.43$, $p < 0.05$). This association was found to be stronger among smokers. A positive correlation between lung function and some pro-inflammatory cytokines (IL-2, IL-4, IL-8, and TNF α) was also observed.

4 CONCLUSIONS

To our knowledge, our study is the first to demonstrate a protective effect of vit. D on lung function in a population chronically exposed water As. The study has several strengths including multiple measures of As exposure including water and urine samples, and measurement of post-bronchodilator lung function tests to assist in establishing the presence of reversible

obstructive lung disease. Our analysis also reveals an As-associated immune modulation which may explain part of As related non-malignant respiratory outcomes. Findings from our study may have important public health implication in As exposed populations around the globe.

ACKNOWLEDGEMENTS

This work was supported by US NIEHS grants P42 ES10349, P30 ES 09089, R01 ES019968-02S1 and R01 ES023888. Thanks to our field staff and the study participants.

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