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What is the role of obesity in the aetiology of arsenic-related disease?

Zhijie M. Yu [a], Bryan Fung [b], John D. Murimboh [b], Louise Parker [a], Trevor J.B. Dummer [a,*]

[a] Population Cancer Research Program and Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, B3H 4R2, Canada
[b] Department of Chemistry, Acadia University, Wolfville, Nova Scotia, B4P 2R6, Canada

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ABSTRACT

Consumption of arsenic contaminated drinking water causes a large variety of adverse health outcomes. Body mass index (BMI), which is linked to diet, is positively associated with arsenic methylation capacity. We investigated the association between an obesity-related diet and arsenic body burden from exposure to naturally contaminated drinking water among Nova Scotia residents. We collected home drinking water and toenail clipping samples among 960 men and women aged 35 to 69 years in Nova Scotia, Canada from 2009 through 2010. We measured body composition and arsenic concentrations in drinking water and toenails clipping samples and collected socio-demographic, behavioural, and dietary information *via* standardized questionnaires. We derived an obesity-related dietary pattern score using reduced rank regression. Across quartiles of the obesity-related dietary pattern score there were no significant differences in drinking water arsenic concentrations, but there was an inverse trend in arsenic concentrations in toenails across the dietary pattern score ($P = 0.01$). Compared with individuals in the first quartile of the dietary pattern score, those in the second through fourth quartiles had decreased likelihoods of high toenail arsenic (≥85 percentile). The corresponding odds ratios (95% confidence intervals [CI]) were 0.81 (95% CI, 0.49, 1.36), 0.57 (95% CI, 0.33, 0.99), and 0.55 (95% CI, 0.31, 0.98), respectively (P for trend $= 0.02$). We conclude that given similar levels of naturally occurring arsenic exposure *via* drinking water, an obesity-related dietary pattern was associated with significantly lower arsenic concentrations in toenails. Further studies to investigate the underlining mechanisms are warranted.

1. Introduction

Despite the fact that hundreds of millions of people worldwide are exposed to drinking water that is naturally contaminated with inorganic arsenic (Nordstrom, 2002), the influence of lifestyles on arsenic metabolism in humans is not well understood. Arsenic is a ubiquitous metalloid in the Earth's crust and a known human carcinogen (Hughes et al., 2011). Substantial evidence suggests that long-term exposure to arsenic is associated with increased risk of developing skin, lung, liver, bladder, and kidney cancers (Hughes et al., 2011; Smith et al., 1992). Recently, a growing body of evidence has shown that low to moderate levels of arsenic from drinking water (<500 μg/L) (Hughes et al., 2011; Yoshida et al., 2004) may lead to the occurrence of a large variety of chronic illnesses, including major cardiometabolic diseases (hypertension, coronary heart disease, stroke, and diabetes mellitus) and diseases of the reproductive, neurological, respiratory, hepatic, and hematological systems (Naujokas et al., 2013; Rahman et al., 2009; Yoshida et al., 2004).

In North American populations with low-to-moderate arsenic exposure from drinking water, arsenic in toenail clippings, as a biomarker of arsenic body burden, has been found to be associated with increased cancer risk (Heck, 2009; Karagas et al., 2004). Though arsenic in toenails is a proxy of arsenic exposure from the total environment, arsenic in drinking water has been shown to have the strongest association with arsenic in toenails among various exposure pathways (Hinwood et al., 2003; Slotnick et al., 2007). These phenomena may be attributed to both the biological characteristics of toenails and the major exposure routes of inorganic arsenic. Nails contain high concentrations of keratin which has strong affinity for inorganic arsenic (Hughes, 2006; Mandal et al., 2003), but once expelled from the nail bed nails are isolated from the body's metabolic activities (He, 2011). Compared with fingernails, toenails have a relatively slower growth rate that may represent a long-term exposure and are less likely to be exposed to external contamination (Garland et al., 1993; He, 2011). With respect to exposure pathways, an American study (Meliker et al., 2006) showed that home drinking water was the major source of inorganic arsenic exposure accounting for ~55% in the intake variance. Food intake was the second explaining ~37% of the variance.

Studies have shown that body mass index (BMI), as an indicator of overall nutritional status, is positively associated with arsenic methylation capacity (Gomez-Rubio et al., 2011; Lindberg et al., 2007; Tseng

Abbreviations: BMI, body mass index; CI, confidence interval; CPTP, Canadian Partnership for Tomorrow Project; DMA, dimethyl arsenic; FFMI, fat free mass index; FFQ, food frequency questionnaire; FMI, fat mass index; ICP-MS, Inductively Coupled Plasma-Mass Spectrometer; IPAQ, International Physical Activity Questionnaire; MDL, method detection limit; MMA, monomethyl arsenic; OR, odds ratio; PATH, Partnership for Tomorrow's Health; RCS, restricted cubic spline; RRR, reduced rank regression.

* Corresponding author at: 1494 Carlton Street, PO Box 15000, Halifax, NS, B3H 4R2, Canada. Tel.: +1 902 494 8059; fax: +1 902 494 2089.
E-mail address: trevor.dummer@dal.ca (T.J.B. Dummer).

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et al., 2005). Furthermore, arsenic-related skin lesions, such as melanosis and keratosis, have been found to be more prevalent among individuals with lower levels of BMI (<18.5 kg/m^2) compared to those with normal BMI in arsenic-endemic areas in Bangladesh (Ahsan et al., 2006) and Pakistan (Fatmi et al., 2009), suggesting that there may be greater arsenic retention in lower BMI individuals. However, the role of body adiposity in arsenic methylation remains unclear (Tseng, 2009). In our previous analyses with accurately measured body composition, both fat mass and fat free mass were inversely associated with arsenic in toenails (Yu et al., 2013). Physical activity, an important factor related to body weight, was not associated with arsenic in toenails. We, therefore, hypothesized that other factors related to increased body weight might play a role in our observed associations.

It is widely recognized that dietary factors play an important role in the aetiology of obesity development (Haslam and James, 2005). A recent study reported that total fat and protein intake was inversely associated with toenail arsenic concentrations in an American population (Gruber et al., 2012), indicating dietary factors leading to increased body weight may be involved in arsenic metabolism. Similarly, in the western US, Steinmaus et al.(2005) found that individuals in the lower quartile of protein intake had significantly higher proportions of monomethyl arsenic (MMA) and lower proportions of dimethyl arsenic (DMA) in urine than their counterparts in the upper quartile, suggesting reduced arsenic methylation capacity among those with lower levels of protein intake. Likewise, in Bangladesh, a study reported that protein intake was negatively associated with MMA and positively associated with DMA in urine (Heck et al., 2007). Individuals with higher levels of protein intake have been shown to excrete more arsenic in their urine compared with those with lower levels of protein intake and this association was independent of arsenic exposure from drinking water (Heck et al., 2009). In contrast, two studies carried out among people living in arsenic-endemic areas observed that neither overall protein consumption (McCarty et al., 2006), nor a dietary pattern featuring animal protein (Pierce et al., 2011), had any impact on risk of developing skin lesions, suggesting that other factors associated with protein intake may be involved in modulating arsenic toxicity.

The aim of the present study was to investigate whether a dietary pattern associated with obesity might mediate the relationship between arsenic in drinking water (arsenic exposure) and arsenic in toenail clippings (arsenic body burden) among a cohort of Nova Scotia residents. We hypothesize that a dietary pattern related to increased body weight might be associated with reduced arsenic body burden among people exposed to arsenic *via* both drinking water and diet.

2. Materials and methods

2.1. Study population

The Atlantic PATH (Partnership for Tomorrow's Health) cohort study is a part of the Canadian Partnership for Tomorrow Project (CPTP), a national study examining the role of genetic, environmental, behavioural, and lifestyle factors in the development of cancer and chronic disease (Borugian et al., 2010). The detailed methods on participant recruitment and data collection have been described previously (Yu et al., 2013). In brief, Atlantic PATH is a population-based cohort with participants recruited from the Atlantic Canada Provinces (Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland and Labrador) and aged between 35 and 69 years. The study subjects of this analysis were individuals who participated in the Atlantic PATH Nova Scotia Arsenic Sub-Study and provided both drinking water samples and toenail clippings at the Sydney and Halifax assessment centres in Nova Scotia from 2009 through 2010. The present analysis includes 960 participants who have had both drinking water and toenail clipping samples analysed for trace elements, including arsenic. The study protocol was approved by the Capital District Health Authority and Cape Breton District Health Authority Research Ethics Boards.

2.2. Data collection

We instructed participants on how to collect, store, and return water samples. Participants were asked to run the water tap for 10 min to flush the system, fill the sample bottle until it overflowed to eliminate air gaps and store the sample in a refrigerator prior to returning to the study team. During attendance at an assessment centre, toenail clipping samples were collected by trained staff. Participants completed a set of standardized questionnaires on socio-demographic, health, diet, and lifestyle factors. Research nurses carried out physical measurements for the participants, including anthropometric indices and body composition.

2.2.1. Assessment of water sample source

Water samples were collected predominantly from the participants' principle residence, although some participants provided a sample from a second home if that water supply was from a well. Water sources were classified as municipal treated water, private drilled well, private dug well, and other (including natural spring, lake, river, lagoon, dugout, and other unspecified sources). Because very few participants reported the type of water treatment system that was in use, well water treatment use was grouped as either yes, no, or unknown.

2.2.2. Measures of anthropometric indices and body composition

Body weight, percentage body fat, fat mass, and fat free mass were measured using the Tanita bioelectrical impedance device (Tanita BC-418, Tanita Corporation of America Inc., Arlington Heights, Illinois) (Beeson et al., 2010; Jebb et al., 2000). Body height was measured by a Seca stadiometer. BMI was calculated as weight in kilograms divided by height in metres squared. Fat mass index (FMI) and fat free mass index (FFMI) were calculated by dividing fat mass and fat free mass in kilograms by height in metres squared, respectively (Schutz et al., 2002). Waist circumference was measured by using a Lufin steel tape. Overweight was defined as 25 ≤ BMI < 30 kg/m^2 and obesity was defined as BMI ≥ 30 kg/m^2. Abdominal obesity was defined as waist circumference ≥ 102 cm for men and ≥ 88 cm for women (Grundy et al., 2005).

2.2.3. Arsenic concentrations in drinking water and toenail clipping samples

Arsenic concentrations in drinking water were determined by adapting US EPA method 200.8. Samples were acidified to 1% (v/v) with ultrapure nitric acid (Fisher Optima grade) and analysed using a PerkinElmer Elan DRC-*e* Inductively Coupled Plasma-Mass Spectrometer (ICP-MS) equipped with an SC4 DX autosampler (ESI). Arsenic was measured in dynamic reaction cell mode using oxygen as a reaction gas. Coefficients of variation were typically < 0.12 for arsenic concentrations < 1.0 μg/L and < 0.05 for concentrations ≥ 1.0 μg/L. Certified Reference Materials (CRMs) NIST 1643e (Trace elements in drinking water) and SLRS-4 (Trace elements in river water) were analysed for each batch to assess the accuracy of the method.

Toenail samples were prepared according to the method of Ryabukhin (1980) and then digested by adapting the method of Gault et al. (2008). The digested toenail samples were analysed using a PerkinElmer Elan DRC-*e* ICP-MS equipped with an SC4 DX autosampler (ESI). Arsenic was measured in dynamic reaction cell mode using oxygen as a reaction gas. Coefficients of variation were typically <0.10 for arsenic concentrations <0.3 μg/g and <0.05 for concentrations ≥0.3 μg/g. CRM NCS DC73347a / GBW 07601 (Trace elements in human hair) was used to assess the accuracy of the method for each batch.

Method detection limits (MDLs) were calculated for each batch of the measurements. The average MDLs were 0.066 μg/L for water samples and 0.046 μg/g for toenail samples, respectively. Those arsenic