Environmental Research 131 (2014) 131–133

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Reports from the Field

Inverse association between toenail arsenic and body mass index in a population of welders

Rachel Grashow [a,*], Jinming Zhang [a], Shona C. Fang [a,b], Marc G. Weisskopf [a,c], David C. Christiani [a,c], Molly L. Kile [d], Jennifer M. Cavallari [a,e]

[a] Department of Environmental Health, Harvard School of Public Health, Landmark Center, 401 Park Drive, 3rd Floor, Boston, MA 02215, USA
[b] New England Research Institutes, Watertown, MA, USA
[c] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
[d] Department of Public Health, College of Public Health and Human Sciences, Oregon State University, Corvallis, OR, USA
[e] Division of Occupational and Environmental Medicine, University of Connecticut Health Center, Farmington, CT, USA

ARTICLE INFO

Article history:
Received 13 November 2013
Received in revised form
14 February 2014
Accepted 11 March 2014
Available online 9 April 2014

Keywords:
Arsenic
Toenail
BMI
Welding fume
Metals
Occupational health

ABSTRACT

Recent data show that arsenic may play a role in obesity-related diseases. However, urinary arsenic studies report an inverse association between arsenic level and body mass index (BMI). We explored whether toenail arsenic, a long-term exposure measure, was associated with BMI in 74 welders with known arsenic exposure. BMI showed significant inverse associations with toenail arsenic ($p=0.01$), which persisted in models adjusted for demographics, diet and work history. It is unclear whether low arsenic biomarker concentrations in high BMI subjects truly reflect lower exposures, or instead reflect internal or metabolic changes that alter arsenic metabolism and tissue deposition.

1. Introduction

In the United States, arsenic exposure may result after drinking As-rich well water, or eating arsenic-rich food such as rice (Yost et al., 1998). Occupational exposure to arsenic can also occur. Welders are exposed to heavy metal particulates including arsenic when molten metal is volatilized during weld tasks or when working in coal-fired power plants. Once ingested or inhaled, inorganic arsenic (iAs) undergoes a methylation process in the liver, whereby it is converted into monomethylarsenate (MMA) and then to dimethylarsinate (DMA). The relative distributions of these metabolites (iAs, MMA, and DMA) in urine are seen as good markers of internal dose resulting from exposure occurring within three days of sampling. They can also be used to evaluate an individual's ability to metabolize arsenic which is a risk factor for disease (Chen et al., 2005).

As an alternative to urinary metabolites, toenail clippings are another non-invasive way to quantify internal arsenic dose over intermediate time scales. They provide a historical cumulative record of previous arsenic exposure because they represent exposures occurring 6–12 months prior to clipping (Grashow et al., 2013; Laohaudomchok et al., 2011; Longnecker et al., 1993). As such, toenail arsenic (TnAs) concentrations may be more appropriate for evaluating the association between arsenic exposure and chronic health conditions.

Two recent studies have shown inverse relationships between body mass index (BMI) and urinary arsenic biomarkers. In women, higher BMI was associated with increased arsenic methylation efficiency, as reflected by higher ratios of urinary DMA to MMA ratios, and lower percentages of MMA excreted in urine (Gomez-Rubio et al., 2011). In a different study on a population of Taiwanese adolescents, total urinary arsenic was significantly lower in subjects with higher BMI (Su et al., 2012). In addition, a large study conducted in New Hampshire residents (Gruber et al., 2012) proposed that dietary fat may inhibit arsenic absorption because it was observed that TnAs decreased with increased dietary fat intake. Taken together, these studies imply that arsenic uptake, metabolism and excretion may be influenced by body mass index and dietary fat intake.

Given the interest in the potential for arsenic to influence obesity-related diseases (Maull et al., 2012; Navas-Acien et al., 2008) it is important to further examine the relationship between arsenic exposure and body composition measures. Additional arsenic–BMI studies will only improve our understanding of a commonly used

* Corresponding author. Fax: +1 617 384 8994.
E-mail address: rgrashow@hsph.harvard.edu (R. Grashow).

http://dx.doi.org/10.1016/j.envres.2014.03.010
0013-9351/

confounding variable, which may not be a straightforward reflection of internal dose. We hypothesized that internal dose of arsenic, as measured by toenails, would be inversely associated with BMI after adjusting for dietary fat intake. We tested this hypothesis in a population with both occupational and background environmental arsenic exposures.

2. Methods

As previously described (Grashow et al., 2013), study participants ($n=74$) were recruited from active and retired members of a boilermakers' union located in Quincy, MA. Boilermakers are welders trained to weld round vessels and pipes located within power plants. Participants were monitored at the union hall over two winter and two summer sampling periods from 2010 to 2011, with some subjects participating over multiple study visits. Height and weight were measured on site, and used to calculate BMI (kg/m^2). All 10 toenails of study subjects with adequate toenail growth at the time of the site visit were clipped, which were combined in an envelope. Subjects without adequate toenail growth were given stamped addressed envelopes to be returned after clipping. The study protocol was approved by Harvard School of Public Health Institutional Review Board and written informed consent was given prior to participation.

External contamination was removed from toenail clippings using a washing protocol and analyzed for total arsenic using a dynamic reaction cell-inductively coupled plasma mass spectrometer (DRC-ICP-MS, Elan 6100, PerkinElmer, Norwalk, CT) as previously described (Kile et al., 2007). All participants completed questionnaires related to lifestyle variables, medical history and demographics. A standard food frequency questionnaire (FFQ) was administered to quantify daily consumption of over 100 food items over the previous 12 months, including dietary supplements (Willett et al., 1985). Frequency options ranged from never to six or more times per day. Nutrient composition was quantified (Willett et al., 1987), summed across foods and converted to a daily consumption rate. Retinol values were scaled to 900 mcg of retinol activity equivalents (RAEs), the recommended daily allowance of retinol for adults. Fifty-three welders were given union-supplied lists of completed jobs, with the welders providing specific details on hours welded. These data were used to create variables summarizing total hours welded over 0–12 months and 7–12 months prior to toenail clip date. This simplified work history metric has been previously shown to be associated with toenail metal concentrations (Grashow et al., 2013).

Linear mixed models were used to estimate associations between log-transformed (base 10) TnAs and BMI. Mixed models were used in all analyses to account for any within subject correlation that occurred with the use of multiple toenail samples for some subjects. Age, smoking status, season of toenail clipping and dietary factors were added to the model to determine their relationship with toenail arsenic and to evaluate if they alter the association between TnAs and BMI. Given that the participants may have been exposed to arsenic during welding tasks or while at coal-powered plants, a sensitivity analysis was performed using work history data from 12 months prior to toenail clipping among the 53 welders with these data.

3. Results

Seventy-four male subjects provided a total of 133 toenail samples, and subject characteristics are summarized in Table 1. The average age at first participation was 42.0 years (standard deviation [SD]=13.4), with 10.8 (6.4) years experience as a welder. The average body mass index (BMI) was 29.4 (6.4) kg/m^2. Approximately 35% of all subjects were current cigarette smokers, and 85% were white. Average toenail arsenic was 0.18 (0.15) μg/g toenail. Forty-one subjects provided one toenail sample, while 33 subjects provided two or more.

Table 1
Descriptive statistics for study participants ($n=74$).

Characteristic	*n*	Mean	SD
Age at first participation (years)	74	42.9	13.5
Body mass index (kg/m^2)	74	29.4	6.5
Years as a boilermaker (years)	73	11.0	10.5
TnAs (μg/g)	74	0.18	0.15
Alcohol (drinks per week)	74	19.4	33.5
Daily caloric intake (kcal)	74	2275	1273
	n	**%**	
White	63	85	
Current smokers	26	35	
Male	74	100	

There was a statistically significant inverse relationship between log-transformed arsenic and BMI ($\beta=-0.03$, 95% CI: -0.05, -0.01; Table 2, Model 1). This effect was unchanged when age was added to the model (Model 2). Additional adjustment for current smoking status, alcohol use, season of toenail clipping and total caloric intake did not change the association between toenail arsenic and BMI or age (Table 2, Model 3).

We found a positive association between omega-3 fatty acid (g) intake and TnAs (β: 0.04, 95% CI: 0.001, 0.08, $p=0.04$). In this model, the parameter estimate for BMI was approximately equivalent to the unadjusted model of toenail arsenic (Model 1, Table 2). We found a positive association between α-linolenic acid (g) and toenail arsenic (β: 0.39, 95% CI: 0.11, 0.67, $p=0.007$). In this model, the term quantifying the association between BMI and toenail arsenic remained similar to those of previous models. Finally, we found a small but significant positive association between the RDA for retinol (IU), a vitamin A derivative and toenail arsenic (β: 0.16, 95% CI: 0.04, 0.28, $p=0.01$).

No other metal measured in this population (lead, manganese, cadmium or nickel) was associated with BMI (data not shown). In separate linear mixed models that included either the hours welded summed over 7–12 or 0–12 months, the parameter estimate for BMI in relationship to TnAs grew slightly larger and remained significant (β: -0.04, 95% CI: -0.08, -0.01, $p=0.02$), while total hours welded was not significantly associated with TnAs (1–12 months: β: 0.00003, 95% CI: -0.0007, 0.001, $p=0.94$; 7−12 months: β: 0.0001, 95% CI: -0.0004, 0.001, $p=0.68$). These models were adjusted for age, caloric intake, alcohol intake, season of toenail collection and smoking.

4. Discussion and conclusions

We found a consistent inverse relationship between log-transformed toenail arsenic concentration and BMI. This relationship was independent of dietary intake of omega-3 fatty acid, alpha-lineolenic acid, and retinol, the only dietary nutrients found to be significantly associated with TnAs. These results complement previous studies that show an inverse relationship between BMI and total urinary arsenic (Gomez-Rubio et al., 2011; Su et al., 2012).

In a large study of New Hampshire residents, Gruber et al. (2012) found that average TnAs concentrations were lower than those seen in the welder population described here (0.12 ± 0.14 ([NH] vs. 0.18 ± 0.14 [MA] μg/g). In the Normative Aging Study, a community-wide longitudinal study on aging in men from the greater Boston area, the median toenail arsenic value was 0.08 μg/g (Mordukhovich et al., 2012), which is lower than the median in the welder population participating in this study (0.14 μg/g). Most likely, these higher toenail arsenic values seen in the welding cohort result from occupational exposure to arsenic that occurred in addition to background environmental arsenic exposure. This could occur despite the lack of association between TnAs and total work hours, which may not be picked up by the simple total work hour metric which did not specifically account for time spent in coal-fired power plants.

Gruber et al. proposed that dietary fat may inhibit arsenic absorption because they observed that TnAs decreased with increased dietary fat intake. Interestingly, most dietary associations seen in the New Hampshire study (dietary fats, animal protein and vitamin B12) were not observed in this occupational cohort. These differences could be due to the smaller size of this cohort, additional occupational arsenic exposure seen in welders,

Table 2
Parameter estimates, 95% CI and *p*-values for models of log-transformed toenail arsenic concentration and BMI ($n=133$).

Model	BMI			Age			Dietary factor		
	β	95% CI	*p*-value	*β*	95% CI	*p*-value	*β*	95% CI	*p*-value
1	−0.04	(−0.06, −0.01)	0.004	-			–		
2	−0.03	(−0.05, −0.01)	0.006	−0.02	(−0.03, −0.01)	0.002	–		
3	−0.03	(−0.05, −0.01)	0.011	−0.02	(−0.03, −0.01)	0.003	–		
4	−0.03	(−0.06, −0.01)	0.006	−0.02	(−0.03, −0.01)	0.002	0.39	(0.11, 0.669)	0.007
5	−0.03	(−0.06 ,−0.01)	0.007	−0.02	(−0.03, −0.01)	0.003	0.04	(0.001, 0.08)	0.044
6	−0.03	(−0.06, −0.01)	0.006	−0.02	(−0.03, −0.01)	0.003	0.16	(0.035, 0.283)	0.013

Model 1: unadjusted.
Model 2: same as model 1, additionally adjusted for age.
Model 3: same as model 2, additionally adjusted for caloric intake, alcohol (g), current smoking status, season of toenail clipping.
Model 4: same as model 3, additionally adjusted for α-linolenic fatty acid (g).
Model 5: same as model 3, additionally adjusted for omega-3 fatty acid (g).
Model 6: same as model 3, additionally adjusted for retinol (per 900 mcg RAE, the retinol RDA for adults).

or the insufficient adjustment for BMI in the New Hampshire cohort resulting from missing data. Elucidating the role of dietary factors either as a source of arsenic or as a source of nutrients for arsenic metabolites requires longitudinal studies to further unravel these potential competing pathways.

The association observed in this occupational cohort between BMI and TnAs may be due to drinking water and dietary habits that are also related to BMI. It is possible that participants with higher BMI consume fewer high arsenic foods and subsequently have lower arsenic exposure. It is also plausible that heavier individuals ingest more co-factors utilized in arsenic metabolism such as methionine, vitamin B12 and folic acid which influence arsenic excretion and distribution into toenail, although associations between TnAs and these co-factors were not seen in this study or in the Gruber et al. (2012) study. Changes in metabolic function associated with high BMI could also be partially responsible for differences seen in arsenic metabolism, resulting in differential toenail tissue arsenic deposition. Recent papers show that heavier adults and teens have different percentages of urinary arsenic metabolites (Gomez-Rubio et al., 2011; Su et al., 2012), which may imply alterations in metabolism or differences in nutrient intake that affect how arsenic is methylated and excreted.

A recent article found that the absolute daily inhalation rates of overweight or obese individuals were greater than in normal weight subjects, indicating higher exposures to air pollutants (Brochu et al., 2014). If we assume the same to be true in the cohort described here, we would expect to see higher arsenic concentrations in toenails from heavier subjects. However, we saw lower toenail arsenic in subjects with higher BMI, further indicating that arsenic disposition in nail tissue may not directly reflect internal dose.

There are a number of limitations to this study. Toenail arsenic measures only quantified total arsenic, so the relative distributions of MMA and DMA are unknown. Food frequency questionnaires may be subject to recall bias, omit relevant food sources, and can include error in the calculation of specific nutrients from reported food frequencies. In addition, our population was small but the repeated measures of exposure from multiple toenail samples were provided by 56% of the population, reducing variability in TnAs concentrations. Finally, the results described here may be applicable only to populations who consume a Western diet. While we lack mechanistic data to determine the underlying cause of the inverse BMI–TnAs relationship, these data in conjunction with other studies raise the question of whether biomarkers of arsenic in subjects with a wide range of BMIs truly measure exposure or dose. Future studies that utilize arsenic biomarkers would benefit from a deeper understanding of how body composition may alter how the body absorbs, metabolizes, distributes, and excretes arsenic.

Acknowledgments

The authors thank the International Brotherhood of Boilermakers, Local No. 29, Quincy, MA. This research was supported by the National Institute of Environmental Health Sciences (NIEHS) grants under Grants ES009860, ES00002, T32 ES7069, and K01 ES017800, a Young Clinical Scientist Award from the Flight Attendants Medical Research Institute (FAMRI), and a Scientist Development Grant from the American Heart Association (AHA). Additional support was provided by the Center for Construction Research and Training (CPWR) through the National Institute for Occupational Safety and Health (NIOSH) cooperative agreement OH009762. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIEHS/NIH, CPWR, AHA, or NIOSH.

References

Brochu, et al., 2014. Physiological daily inhalation rates for health risk assessment in overweight/obese children, adults, and elderly. Risk Anal. 34, 567–582.
Chen, C.J., et al., 2005. Biomarkers of exposure, effect, and susceptibility of arsenic-induced health hazards in Taiwan. Toxicol. Appl. Pharmacol. 206, 198–206.
Gomez-Rubio, P., et al., 2011. Association between body mass index and arsenic methylation efficiency in adult women from southwest U.S. and northwest Mexico. Toxicol. Appl. Pharmacol. 252, 176–182.
Grashow, R., et al., 2013. Toenail metal concentration as a biomarker of occupational welding fume exposure. J. Occup. Environ. Hyg. (epub ahead of print).
Gruber, J.F., et al., 2012. Associations between toenail arsenic concentration and dietary factors in a New Hampshire population. Nutr. J. 11, 45.
Kile, M.L., et al., 2007. Association between total ingested arsenic and toenail arsenic concentrations. J. Environ. Sci. Health A 42, 1827–1834.
Laohaudomchok, W., et al., 2011. Toenail, blood, and urine as biomarkers of manganese exposure. J. Occup. Environ. Med. 53, 506–510.
Longnecker, M.P., et al., 1993. A 1-y trial of the effect of high-selenium bread on selenium concentrations in blood and toenails. Am. J. Clin. Nutr. 57, 408–413.
Maull, E.A., et al., 2012. Evaluation of the association between arsenic and diabetes: a National Toxicology Program workshop review. Environ. Health Perspect. 120, 1658–1670.
Mordukhovich, I., et al., 2012. Associations of toenail arsenic, cadmium, mercury, manganese, and lead with blood pressure in the normative aging study. Environ. Health Perspect. 120, 98–104.
Navas-Acien, A., et al., 2008. Arsenic exposure and prevalence of type 2 diabetes in US adults. J. Am. Med. Assoc. 300, 814–822.
Su, C.T., et al., 2012. The relationship between obesity, insulin and arsenic methylation capability in Taiwan adolescents. Sci. Total Environ. 414, 152–158.
Willett, W.C., et al., 1985. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am. J. Epidemiol. 122, 51–65.
Willett, W.C., et al., 1987. Dietary fat and the risk of breast cancer. N. Engl. J. Med. 316, 22–28.
Yost, L., Schoof, R.A., Aucoin, R., 1998. Intake of inorganic arsenic in the North American diet. Hum. Ecol. Risk Assess. 4, 133–152.