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Obesity and increased susceptibility to arsenic-related type 2 diabetes in Northern Chile

Felicia Castriota[a], Johanna Acevedo[b], Catterina Ferreccio[b], Allan H. Smith[c], Jane Liaw[c], Martyn T. Smith[a], Craig Steinmaus[c,d,*]

[a] Environmental Health Sciences Division, School of Public Health, University of California, Berkeley, CA, United States
[b] Pontificia Universidad Católica de Chile, Advanced Center for Chronic Diseases, ACCDiS, Santiago, Chile
[c] Arsenic Health Effects Research Program, School of Public Health, University of California, Berkeley, CA, United States
[d] Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA, United States

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ABSTRACT

Background: The prevalence of type 2 diabetes (T2D) has nearly doubled since 1980. Elevated body mass index (BMI) is the leading risk factor for T2D, mediated by inflammation and oxidative stress. Arsenic shares similar pathogenic processes, and may contribute to hyperglycemia and β-cell dysfunction.
Objectives: We assessed a unique situation of individuals living in Northern Chile with data on lifetime arsenic exposure to evaluate the relationship between arsenic and T2D, and investigate possible interactions with BMI.
Methods: We analyzed data collected from October 2007-December 2010 from an arsenic-cancer case-control study. Information on self-reported weight, height, smoking, diet, and other factors were obtained. Diabetes was defined by self-reported physician-diagnoses or use of hypoglycemic medication. A total of 1053 individuals, 234 diabetics and 819 without known diabetes were included.
Results: The T2D odds ratio (OR) for cumulative arsenic exposures of 610–5279 and ≥ 5280 μg/L-years occurring 40 years or more before interview were 0.97 (95% CI: 0.66–1.43) and 1.53 (95% CI: 1.05–2.23), respectively. Arsenic-associated T2D ORs were greater in subjects with increased BMIs. For example, the ORs for past cumulative exposures ≥ 5280 μg/L-years was 1.45 (95% CI: 0.74–2.84) in participants with BMIs < 25 kg/m^2 but 2.64 (95% CI: 1.14–6.11) in those with BMIs ≥ 30 kg/m^2 (synergy index = 2.49, 95% CI: 0.87–7.09). Results were similar when people with cancer were excluded.
Conclusions: These findings identify increased odds of T2D with arsenic exposure, which are significantly increased in individuals with excess BMI.

1. Introduction

More than 200 million individuals worldwide are exposed to arsenic-contaminated drinking water above the World Health Organization (WHO)'s permissible limit of 10 μg/L (Naujokas et al., 2013). Ingested arsenic is an established carcinogen and prevalent at high concentrations in drinking water sources in Taiwan, Bangladesh, India, Chile, Argentina, the US, and elsewhere (ATSDR, 2007; IARC, 2004, 2012). In the US, an estimated 12% of all public water systems have arsenic concentrations near 10 μg/L (U.S. EPA, 2000), the current US regulatory standard. Millions more people are likely exposed to even higher arsenic water concentrations from private wells, which are not regulated (Steinmaus, 2005). Arsenic also occurs in apple juice, chicken, wine, and beer (Marshall, 2012; Nachman et al., 2013; Schute, 2013; Wilson et al., 2012), and the US Food and Drug Administration (FDA) found arsenic in almost all 193 brands of rice, rice baby foods, and rice cereals tested (U.S. FDA, 2012). Arsenic is also common at industrial waste sites and is currently ranked first on the Superfund hazardous waste site priority list in terms of toxicity and prevalence of exposure (ATSDR, 2013).

Type 2 diabetes (T2D) is a chronic condition of increasing prevalence, affecting an estimated 415 million individuals worldwide, projected to increase to 642 million by the year 2040 (Zimmet et al., 2016). In Chile, the prevalence of diabetes mellitus has increased from 4.2% in 2003 to 12.3% in 2016 (Ministerio de Salud, 2017). Although obesity is the primary risk factor for T2D, other factors may also play a role in either directly causing T2D or in enhancing the role of excess BMI on T2D risks (Thayer et al., 2012). Arsenic has been linked to T2D

* Correspondence to: 2470 Telegraph Ave., Suite 301, Berkeley, CA 94704, United States.
E-mail address: craigs@berkeley.edu (C. Steinmaus).

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in areas with high exposures (Huang et al., 2011; Maull et al., 2012), but studies of lower exposures (e.g., < 100 μg/L) have produced very mixed and unclear results (Smith, 2013). Although the primary mechanism of arsenic toxicity is unknown, it has been shown to affect several mechanistic pathways that are linked to both obesity and T2D. For example, both arsenic and obesity have been associated with mitochondrial dysfunction and with increases in reactive oxygen species (ROS), two processes that are thought to play an important role in T2D development (Pan et al., 2016; Tseng et al., 2004; Bournat and Brown, 2010). Given these and other shared pathologic processes, we hypothesized that arsenic and obesity might interact to increase T2D risk.

Many of the water sources in Northern Chile are contaminated with naturally-occurring arsenic, with concentrations ranging from < 10 to > 800 μg/L. This geographical area contains the Atacama Desert, which is the driest inhabited place on earth. Because it is so dry, almost everyone in the area lives in one of the cities or towns in the area, and each city and town has its own single water supply. Extensive historical records of arsenic concentrations in all this area's major water sources are available, and because of this, comprehensive estimates of people's lifetime arsenic exposure, from birth through adulthood, can be made simply by knowing the cities or towns in which they have lived (Ferreccio et al., 2000). These types of lifetime exposure data are not available anywhere else in the world. The largest city in the area, Antofagasta, experienced a period of very high arsenic exposure (average of 860 μg/L) starting in 1958, when two rivers with high arsenic concentrations were diverted to the city for drinking. The high exposures ended in the 1970s, when arsenic treatment plants were installed. Except for the installation of arsenic treatment plants in Antofagasta and several other cities, arsenic concentrations in drinking water have been very stable over time (Ferreccio et al., 2000).

For this paper, we used this unique exposure scenario to assess the effects of arsenic exposure on T2D development, and to evaluate whether arsenic and obesity may act synergistically to increase T2D risk. To our knowledge, the present study is the first to examine the possible interaction between arsenic and obesity on the development of T2D.

2. Materials and methods

2.1. Study area and subject ascertainment

Study design details are published elsewhere (Steinmaus et al., 2013). Briefly, all subjects were participants in an arsenic-cancer case-control study which involved two contiguous regions (Regions I and II) in Northern Chile. Institutional review board approval was obtained in both the US and Chile. Participation was voluntary, and written informed consent was obtained from all subjects or next of kin. Cancer cases in the underlying study included all people who: (i) had newly diagnosed primary lung, bladder, or kidney cancer between October 2007 and December 2010; (ii) lived in Regions I or II at the time of diagnosis; (iii) were > 25 years old when diagnosed; and (iv) were able to provide interview data or had a close relative who could. Cancer cases were ascertained using a rapid case ascertainment system established for the study which involved all pathologists, hospitals, and radiologists in the study area, and most cancer cases were interviewed within three months of diagnosis. Hospital cancer committees and death records were used to identify missing cases. Cancer-free controls, frequency matched to cancer cases by sex and five-year age groups, were randomly selected from the Chile Electoral Registry. This Registry contains > 95% of people over age 50 years based on population numbers for Regions I and II recorded in the Chilean Census.

2.2. Participant interviews

Participants were interviewed in person using a standardized study questionnaire. For deceased participants, we interviewed the next of kin (proxy). Participants were asked to provide all lifetime residences, water sources (e.g., public water, bottled) and water filter use at each residence, and all jobs held for at least six months. Participants were also asked about specific occupational exposures including asbestos, arsenic, silica, and solvents. Questions regarding tobacco smoke included age at which smoking began, periods of no smoking, years smoked, number of cigarettes smoked per day, and childhood or adult secondhand smoke exposure. Participants were also asked about typical water intake, both currently and 20 years ago. Typical dietary intakes in the year preceding interview and 20 years earlier were assessed using a modified version of the National Cancer Institute's Diet History Questionnaire. A 14-point socioeconomic status (SES) scoring system was developed by asking subjects about household items (e.g. computer), cars, and use of domestic help. Information on all medical conditions (e.g. hypertension) and medications were collected. For the analyses presented here, diabetics were defined as people who self-reported physician-diagnosed diabetes or who used a hypoglycemic medication.

2.3. Body mass index (BMI)

All subjects and proxy respondents were asked to provide the subjects' adult height and typical weight at ages 20 and 40. People without cancer were also asked to provide their typical weight in the 10 years preceding the interview, and people with cancer were also asked to provide their typical weight in the 10 years preceding their cancer diagnosis. BMI at each period in time was calculated as weight (kg)/height (m^2). Category cut-off points were based on the WHO definition for overweight and obesity in adults of 25 mg/kg^2 and 30 mg/kg^2, respectively, for both men and women.

2.4. Exposure indices

For each subject, each residence in Chile was linked to a water arsenic measurement for that location and the years the subject lived there. Using this process, we could assign an arsenic concentration to each year of each subject's life. Arsenic water records for all cities and towns in Regions I and II, and for all large cities in Chile outside these regions, were collected from governmental agencies, research studies, and water suppliers (Ferreccio et al., 2000). Overall, arsenic water concentrations could be linked to > 95% of all subject residences. Use of bottled water or sources with reverse osmosis filtering were assigned arsenic concentrations of zero. The yearly arsenic exposure estimates for each subject were then used to calculate several metrics of arsenic exposure. These included lifetime cumulative exposure (the sum of each subjects' yearly water concentrations), average exposure (the mean of all of each subject's yearly water concentrations), and lifetime highest (the single highest arsenic water concentration at any year in a subject's life). Results are given for each of these metrics since it is unknown which might be most strongly associated with arsenic-related diabetes. Forty-year lag periods, which ignored all arsenic exposure in the 40 years preceding cancer diagnosis (for people with incident cancer) or interviews (for people without incident cancer), were applied in some analyses. This was done because exposures in the area were highest > 40 years ago (before arsenic treatment plants were installed in several cities). Category cut-off points are tertiles unless otherwise stated.

2.5. Statistical analysis

Odds ratios (OR) for T2D were calculated using unconditional logistic regression for various categories and metrics of arsenic exposure. No heterogeneity in results was observed by sex in analyses of arsenic and T2D, thus males and females were combined. Our inclusion of lung, bladder and kidney cancer cases from the underlying cancer case-control study could potentially introduce bias if these types of cancers were