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A case-cohort study examining lifetime exposure to inorganic arsenic in drinking water and diabetes mellitus

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ABSTRACT

Background: Consumption of drinking water with high levels of inorganic arsenic (over 500 μg/L) has been associated with type II diabetes mellitus (DM), but previous studies have been inconclusive about risks at lower levels (< 100 μg/L). We present a case-cohort study based on individual estimates of lifetime arsenic exposure to examine the relationship between chronic low-level arsenic exposure and risk of DM.

Methods: This case-cohort study included 141 cases of DM diagnosed between 1984 and 1998 as part of the prospective San Luis Valley Diabetes Study. A comparison sub-cohort of 488 participants was randomly sampled from 936 eligible participants who were disease free at baseline. Individual lifetime arsenic exposure estimates were determined using a methodology that incorporates the use of a structured interview to determine lifetime residence and employment history, geospatial modeling of arsenic concentrations in drinking water, and urine arsenic concentrations. A Cox proportional hazards model with known DM risk factors as time-dependent covariates was used to assess the association between lifetime exposure to inorganic arsenic in drinking water and incident DM.

Results: Our findings show a significant association between inorganic arsenic exposure and DM risk (hazard ratio [HR]=1.27, 95%=1.01, 1.59 per 15 μg/L) while adjusting for ethnicity and time varying covariates age, body mass index and physical activity level.

Conclusions: Exposure to low-level inorganic arsenic in drinking water is associated with increased risk for type II DM in this population based on a comprehensive lifetime exposure assessment.

1. Background

Human exposure to arsenic can occur from many sources including the occupational setting (smeltering and wood preservation),, ingestion of contaminated food, and smoking; however, the majority of exposure is through drinking contaminated water (US EPA, 1988). Previous research has documented a relationship between exposure to high concentrations of inorganic arsenic in drinking water and the risk of type 2 diabetes mellitus (DM) (Lai et al., 1994; Tseng et al., 2000; Rahman et al., 2003; Wang et al., 2003; Chen et al., 2007; Navas-Acien et al., 2008; Del Razo et al., 2011; Jovanovic et al., 2012), but the risk at lower levels is unclear (Chen et al., 2010; Huang et al., 2011). Studies from Asia, where water concentrations of inorganic arsenic can be over 500 μg/L, found consumption of inorganic arsenic in drinking water to be associated with increased risk for DM; however in a recent study by Chen et al., 2010, at levels below 300 μg/L there was no association. Research conducted here in the United States (US), where water arsenic concentrations are typically between 1 and 100 μg/L, have found inconclusive associations between inorganic arsenic exposure and risk for DM (Lewis et al., 1999; Meliker et al., 2007; Zierold et al., 2007). A more recent cross-sectional study using the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample, suggested an increased risk for diabetes with higher arsenic concentrations in urine after adjustment for arsenic contribution from seafood (Navas-Acien et al., 2008). However, Steinmaus et al., 2009 replicated the analysis removing arsenobetaine (arsenic contribution from food) from the arsenic metric and

Abbreviations: DM, type II diabetes mellitus; μg/L, Micrograms per Liter; HR, Hazard ratio; SLVDS, San Luis Valley Diabetes Study; ICP-MS, Ion Chromatography and Inductively Coupled Plasma Mass Spectrometry; TWA, Time weighted average; HPLC, High Performance Liquid Chromatography; GPS, Global positioning system; IQR, Interquartile range; BMI, Body mass index; GIS, Geographic Information System

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found no association with diabetes mellitus. These two sets of findings in the same cohort show how the association between diabetes and inorganic arsenic exposure centers on the exposure definition and assessment lending weight to the need for studies involving comprehensive lifetime exposure assessments.

Potential diabetogenic effects of inorganic arsenic exposure have been described (Tseng, 2004; Izquierdo-Vega et al., 2006; Navas-Acien et al., 2006; Diaz-Villasenor et al., 2007a, 2007b; Paul et al., 2007a; Chen et al., 2009; Lu et al., 2011; Escobar-Garcia et al., 2012), but inconsistency in human studies limits conclusions on the causal association. A systematic literature review examined epidemiologic research relating arsenic exposure and DM in several types of populations (high exposure, general population, and occupational setting) and concluded weaknesses in human studies are due to exposure assessment methods, disease diagnostic criteria, population demographics, study design, and insufficient consideration of other DM risk factors (Navas-Acien et al., 2006). Recently, findings from a workshop established to review the toxicology of arsenic relative to diabetes determined that evidence supporting an association between arsenic exposure <150 μg/L and diabetes is insufficient (Maull et al., 2012). Research such as this study, which is prospective in design, has standard criteria for case definition, and detailed lifetime estimates of individual-level exposure to inorganic arsenic, could help clarify the possibility of an association between arsenic and diabetes at levels <150 μg/L.

2. Methods

2.1. Study sample

The relationship between inorganic arsenic exposures over time and the risk of incident DM was studied using a case-cohort design within the San Luis Valley Diabetes Study (SLVDS). The SLVDS is a population-based prospective study of risk factors for diabetes mellitus (DM) and other related chronic diseases among Hispanic and non-Hispanic white residents of Alamosa and Conejos Counties in south-central Colorado who were 20 to 74 years of age at their initial study visit. Participant recruitment and data collection methods have been previously described (Hamman et al., 1989). In brief, between 1984 and 1988, participants provided clinical, behavioral, and demographic data, and diagnostic assessments including the diagnosis of DM (Hamman et al., 1989). All participants were invited to attend two follow up visits, once between 1988 and 1992 and once between 1997 and 1998 where behavioral, demographic, and clinical assessments were updated with a retention rate of 86 percent. In addition, participants with impaired glucose tolerance at baseline were invited for two additional visits for an abbreviated set of assessments. All participants were followed between clinic visits through 1998 with telephone interviews and searches of vital statistics records to track vital status and underlying cause of death (Hokanson et al., 2002).

SLVDS participants without a history of DM and who tested normal or with impaired glucose tolerance but not with diabetes at baseline ($n=1297$) were eligible for this study. Participants with a documented permanent refusal or lost to follow up ($n=361$) were excluded from selection. The remaining 936 participants were eligible for random selection into the study subcohort ($n=488$) which was disease free at the time of initial enrollment. Cases of DM ($n=141$) included all eligible SLVDS participants with a documented DM diagnosis between their baseline visit and 1998. A DM diagnosis was determined either through self-report on yearly follow-up phone calls (with medical record verification) or during a baseline or follow up clinic visit by an 8-h fasting 75 g oral glucose test using the 1985 World Health Organization criteria for DM (WHO required either a fasting venous plasma glucose greater than or equal to 140 mg/dL or a two-hour glucose level greater than or equal to 200 mg/dL) (Hamman et al., 1989). The total study cohort in this case-cohort design, included 548 subjects including 488 randomly selected subjects, of which 81 developed diabetes, and 60 diabetes cases not initially selected, but included as part of the case-cohort design.

This study was reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB) prior to participant contact or initiating data collection.

2.2. Estimating arsenic exposure

The exposure assessment for this study included a lifetime reconstruction of exposure through a structured interview and geospatial modeling of groundwater inorganic arsenic concentrations which was validated by urinary inorganic arsenic species concentrations.

Study subjects ($n=548$) or designated next of kin of deceased subjects were contacted during the 2007–2009 data collection period by mail with information on the study followed by a call to set up an appointment for an interview and water sample collection at their residence. Data collected during the interview ($n=334$ (next of kin; $n=115$), 61%) included addresses for past residences and workplace/school locations, and history of drinking water consumption at each location. For subjects who were not interviewed ($n=203$, 37%), their residential histories were re-constructed from public assessor records at the county clerk office; however past schooling and employment locations are missing for those subjects. There were 11 (3%) subjects who refused participation in this current study.

Residential water samples (both private well and public water) were collected at time of interview ($n=334$) and analyzed by the chemistry laboratory of the Colorado Department of Public Health and Environment using standard Ion Chromatography (IC) and Inductively Coupled Plasma Mass Spectrometry (ICP–MS) with a detection limit of 1 μg/L. Geographic coordinates were determined with a global positioning system (GPS) unit for all water samples collected at houses supplied by private wells.

In other work we detail our methods and findings specific to the temporal and spatial characterization of groundwater inorganic arsenic concentrations in the SLV (James, 2010). In brief, findings indicate that naturally occurring inorganic arsenic concentrations in 175 groundwater wells monitored from 1982 to 2005 ($n=3759$ samples) by the Bureau of Reclamation are stable over long periods of time (samples collected 1 to 5 years apart $r=0.87$; 5 to 10 years apart: $r=0.89$; 10 to15 years apart: $r=0.89$; 15 to 25 years apart: $r=0.88$) which justifies the use of recently collected inorganic arsenic water concentrations in spatial models to predict historical exposures through drinking water. In brief, there are two aquifers in the SLV (confined and unconfined). Wells drawing water from the unconfined aquifer are used primarily for irrigation whereas wells drawing from the confined aquifer are mostly for domestic use or pasture irrigation (Emery, 1979). Arsenic concentrations in the San Luis Valley ranged from non-detectable to 752 μg/L with a mean concentration of 39 μg/L in domestic wells drawing from the confined aquifer.

We collected characteristics on each of the 595 wells in our dataset including, land use, soil type, well depth, use of an irrigation system, land cover, aquifer depth, and distance to the outer edge boundary of the aquifer. A correlation analysis identified well depth as the only factor significantly associated with arsenic concentration within the well. The spatial variability of inorganic arsenic concentrations in ground water was characterized by testing five separate geospatial models including Kriging with external drift and indicator kringing which both account for well depth. Using a correlation analysis in a 10 percent validation sample of observed and predicted values ($\rho=0.715$; 95%CI=0.67, 0.75) (James, 2010), ordinary kriging was found to be the most accurate model for predicting inorganic arsenic in groundwater at residential locations for each participant.

The exposure matrix characterized each participant's annual exposure to arsenic in drinking water. Each participant had one record per year of life starting at birth through year of diagnosis or 1998, whichever came first. Each year's data included residential, employment, and school location and for each location the number of cups of water and arsenic concentration (either observed, if available, or predicted). A time-weighted average (TWA) was calculated by dividing the cumulative arsenic exposure by the number of years in the subject's lifetime to get an annuitized exposure per year (James, 2010).

We validated the method for estimating past arsenic exposure by regressing speciated arsenic concentrations in 462 historically collected urine samples (collected 1984–1991) on residential arsenic concentrations, residential dose, and total dose estimated at time of urine collection, adjusting for gender and creatinine (James et al., in press) (James, 2010). In brief, the sum of the toxic urine arsenic species (As^{3+}, As^{5+}, dimethylarsinic acid, monomethylarsinic acid) (geometric mean: 16.9 μg/dL; range: non-detectable to 123.0 μg/dL) was most strongly correlated with estimates of residential arsenic concentration (ρ0.55 as opposed to other estimates (residential dose: ρ0.37 and total dose: $\rho=0.39$ Residential drinking water arsenic was used for the TWA arsenic exposure measure.

2.3. Statistical analyses

A Cox proportional hazards model incorporating a robust variance estimator specific for case-cohort study designs (Barlow et al., 1999) was utilized to examine the association between the TWA residential inorganic arsenic exposure and development of DM. The arsenic exposure estimate was scaled to the inter-quartile range (IQR) (15 μg/L). Other continuous covariates were also scaled to the IQR (Lin and Huang, 1995).

Longitudinal data from two to five study visits including information on known risk factors for DM were included for each subject. Variables hypothesized as DM risk factors independent of the mechanistic pathways proposed for arsenic were included in the proportional hazards multivariate model as time-dependent covariates. These variables included: ethnicity (White non-Hispanic: Hispanic), gender (male:female), and socioeconomic status (high $>=$$20,000: low $<$$20,000), first degree family history (no:yes), body mass index (BMI: interquartile rage scaled, median=26.7, IQR=23.8, 29.3), smoker status (no:yes), alcohol consumption