



Association between consumption of private well water contaminated by low levels of arsenic and dysglycemia in a rural region of Quebec, Canada



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ABSTRACT

The association between arsenic (As) exposure and diabetes is not clearly defined for populations exposed to low or moderate levels of inorganic As (iAs) in drinking water ($< 150 \mu\text{g/L}$). In the present study, the relationship between iAs concentration in drinking water (contaminated at a median level of $10.5 \mu\text{g/L}$) or As biomarkers (ie, urine and nails) and diabetes or prediabetes (defined as level of glycosylated hemoglobin - HbA1c – higher than 6%, self-reported diagnosis of diabetes by a physician, or the use of insulin or oral hypoglycemic drugs) was evaluated in 257 adults from Canada. For that we used logistic regression models and reported the odds ratio (OR) comparing participants in the 80th vs 20th percentile of iAs exposure indicators. The association between iAs exposure indicators and HbA1c was also explored for 234 adults and 35 children not taking insulin or oral hypoglycemic drugs using a linear regression analysis. All models were controlled for confounding variables (age, gender, first-degree family history of diabetes, obesity or overweight in adults' model). We attempted to exclude adults with organic arsenic of marine origin in their urine by removing participants with detectable arsenobetaine or arsenocholine in urinary models. iAs biomarkers (toenail and urine) were not associated with diabetes or prediabetes in adults. iAs in well water was associated with a borderline significantly increased odds of diabetes or prediabetes (OR = 2.39; 95% CI: 0.99–5.72). Higher well water iAs concentrations were significantly associated with increased HbA1c in both **adults** and **children** (β : 0.002; $p = 0.041$ and β : 0.003; $p < 0.0001$ respectively). In children, HbA1c was also associated with toenail As concentration (β : 0.18; $p = 0.016$). These results suggest low-level iAs exposure is associated with a continuum of dysglycemia.

1. Introduction

Exposure to arsenic (As) primarily occurs through food, drinking water, soil, and air, (Kendall et al., 2003). For populations dwelling on or near an important geological source of inorganic arsenic (iAs), drinking water could represent the most significant source of As exposure (Health Canada, 2006a).

Chronic exposure to iAs in drinking water is associated with an increased risk of cutaneous, pulmonary, kidney, bladder and hepatic cancer (IARC, 2012). In order to control cancer risk, various organizations have adopted a guideline of $10 \mu\text{g/L}$ for public drinking water supplies, although this standard is not enforceable for private wells in most jurisdictions (Health Canada, 2006b; US EPA, 2001; World health organization, 2003).

Questions remain regarding the extent of non-carcinogenic effects arising from sustained exposure to low iAs concentrations in drinking water and the potential for endocrine disease. In vitro studies have shown an influence of iAs on pancreatic B-cell function via oxidative stress and alteration of glucose uptake and transport, gluconeogenesis,

adipocyte differentiation and Ca^{2+} signaling (Maull et al., 2012). An association between drinking water iAs exposure and type 2 diabetes has been demonstrated in several epidemiologic studies (Agency for Toxic Substances and Disease Registry, 2007; World health organization, 2011; Maull et al., 2012) but populations were primarily exposed to iAs concentrations $\geq 150 \mu\text{g/L}$ and methodological issues pertaining to exposure measurement have been identified (Maull et al., 2012).

Urinary As has been used in epidemiologic studies as a long term biomarker due to its reported stability over time (Navas-Acien et al., 2009). Short half-life and differences in xenobiotic excretion and metabolism across populations and particularly in those afflicted with advanced diabetes unfortunately limit its utility. Others have recommended that future epidemiological studies use as detailed an exposure and environmental assessment as possible (Kile and Christiani, 2008).

Nail As has been used as a biomarker to reflect exposures 6–12 months prior to measurement, (Orloff et al., 2009) although it is considered to need further characterization and validation (Maull et al., 2012). We have previously observed a good correlation between nail As and iAs concentration

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in private well water contaminated at a median level of 10.5 µg/L in a study population from Québec, Canada ($r = 0.63$ and $r = 0.45$ in adults and children respectively). This correlation was stronger than the one observed between urinary As and well water iAs concentration ($r = 0.40$ and $r = 0.07$ in adults and children respectively; Gagnon et al., 2016).

In the present study, we evaluate the association between well water iAs concentration and biomarkers of chronic exposure (As in urine and nails) and the prevalence of diabetes and prediabetes, two conditions on a spectrum of dysglycemia, in a population exposed to low-moderate As in drinking water from Quebec, Canada (Canadian Diabetes Association, 2013; Gagnon et al., 2016).

2. Methods

2.1. Study population and recruitment of subjects

This study concerns a population of private well owners and their families living in the Abitibi-Témiscamingue region of Quebec, Canada.

On the basis of a previous screening campaign, three groups of private wells were established: Group 1 with iAs levels < 10 µg/L, Group 2 with iAs levels between 10 and 20 µg/L, and Group 3 with iAs levels ≥ 20 µg/L (Poissant, 1997). Of the 400 households initially available for the first group, 150 were randomly selected. For the second group, all of the 67 potential households were included. The 121 potential households from the third group and 18 new households (unknown previous concentration because not in the initial screening campaign) were all included.

To be eligible, interested individuals had to live in a home supplied by a private well, had to drink or use this water for preparing beverages and food for at least one month, and had to be 7 years of age or older. Those who had an As treatment system, who were occupationally exposed, or who consumed homeopathic medications or herbal dietary supplements were excluded. Pregnancy, kidney or liver diseases, and active cancer were also considered as exclusion criteria. Participants were recruited via telephone.

Out of the initial 489 potential individuals living in the 356 selected households, 71 were uninterested, 69 were ineligible and 54 withdrew because they changed their mind during the interval between the phone call and the home visit. However, 9 were added to the list. In the end, 261 adults and 43 children were recruited in 153 households.

All participants completed a consent form. A child consent form was created for those under 18 years of age, and for which the signature of a legal guardian was also mandatory. This project was approved by Health Canada's Research Ethics Board and by the Human Research Ethics Board at the Centre Hospitalier Universitaire de Sherbrooke (CHUS).

2.2. Variables and data collection

During the first home visit, a project agent recorded age, gender and smoking habits of participants. The materials required for a first morning urine void and toenail clippings were delivered to each of them. Participants received instructions to wash their feet, remove varnish from their toenails and clean them with a brush and a nail file before sampling. A 125 ml sample of well water was taken from the most frequently used tap in an amber bottle containing 1.25 ml of ethylenediaminetetraacetic acid (EDTA). The water samples were temporarily refrigerated before being shipped with icepacks in Styrofoam coolers to the Centre d'expertise en analyse environnementale du Québec (CEAEQ).

During a second home visit, a nurse recorded the participants' medical history, measured their anthropometric parameters (weight, height, waist circumference), took a blood sample for a glycosylated hemoglobin (HbA1c) measurement and collected their urine and toenail samples. Urine samples were then frozen (−20 °C) and toenails refrigerated (4 °C) until they were shipped in coolers with icepacks to the Institut national de santé publique du Québec (INSPQ) human toxicology branch's laboratory.

For the preparation and shipment of blood samples, an agreement

was reached with local laboratories. The tubes for HbA1c were inverted immediately after collection and stored at 4 °C during shipment. These tubes were then shipped to the Centre hospitalier de l'Université de Montréal (CHUM) laboratory within a maximum of two days of handling. The tubes used contained activating silica polymer gel and came with a splatter-free closure.

2.3. Arsenic and glycosylated hemoglobin measurements

The oxidized forms of iAs in water (As^{III}, As^V) were measured at CEAEQ using high performance liquid chromatography with inductively coupled plasma mass spectrometry (CEAEQ, 2008; Garbarino et al., 2002). The total iAs value for well water was determined by adding the As^{III} and As^V values. As for the urine samples, the two forms of iAs (As^{III} and As^V) and their metabolites, namely monomethylarsonic acid (MMA) or dimethylarsinic acid (DMA), as well as arsenocholine and arsenobetaine were all measured (Calderon et al., 1999). Arsenic speciation being difficult to conduct in nails (Maull et al., 2012), total As concentrations (i.e. sum of all species) were measured in the nail samples from the big toe. Gas chromatography extraction and ICP-MS (Inductively Coupled Plasma Mass Spectrometry: M-559 method) identification procedures were used for the analyses of the urinary and nail samples (Belanger and Dumas, 2010; analysis standard: ICP-MS 1, "Multi Element Standard", 10 µg/ml, SCP Science # 140-110-011). Urinary creatinine was measured using colorimetry.

For water, urine or nail samples with levels below the limit of detection (or LD; i.e. 5 µg/L and 0.7 µg/L for each chemical speciation in water and urine respectively and 0.1 µg/g in nails), an imputed value of LD/√(2) was used. This was the case for 70 wells (46% of samples; for both As^{III} and As^V). Almost all the values in the form of DMA were above the LD in adults (98.5%) and children (97.7%). By contrast, practically all the values for As^V were below the LD in adults (98.1%) and children (100%). Urinary As concentration was then calculated by adding As^{III}, MMA, and DMA, adjusted for creatinine. Fifty-five adults (21.1%) and 1 (2.3%) child among the recruited participants had toenail As concentrations below the LD.

HbA1c was measured using HPLC (high performance liquid chromatography) on a Tosoh G7 analyser in the CHUM clinical biochemistry laboratory.

2.4. Diabetes or prediabetes definitions

The prevalence of diabetes or prediabetes was defined by a self-reported prior diagnosis of diabetes by a physician, the use of insulin or oral hypoglycemic drugs, or the presence of an HbA1c level greater than 6%. This HbA1c limit was selected because of its relatively high sensitivity (78–81%) and specificity (79–84%) (Bennett et al., 2007) and use for prediabetes diagnosis (Canadian Diabetes Association, 2013).

2.5. Data analysis

Adult diabetic and prediabetic participants were compared to normoglycemic participants by using a Pearson's chi-squared test for sociodemographic characteristics and a *t*-test for arithmetic mean of clinical characteristics or exposure levels. Given the collinearity (0.87 in adults and 0.92 in children) between waist circumference and body mass index (BMI), the latter variable was prioritized to ensure uniformity with the approach reported in the literature (Navas-Acien et al., 2008). The BMI was categorized in three groups: < 25, 25 to < 30 (overweight) and ≥ 30 (obesity) for all regression analysis.

The association between the prevalence of prediabetes or diabetes and the different exposure levels (80th vs. 20th percentiles of well water iAs concentration, urinary As adjusted for creatinine or toenail As concentration; Models 1, 2 and 3 respectively) was evaluated by determining the odds ratio using a logistic regression analysis while controlling for potential confounding variables (age, gender, BMI, and

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