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Delineating the degree of association between biomarkers of arsenic exposure and type-2 diabetes mellitus

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ABSTRACT

Non-carcinogenic effects in low-level (<100 μg L^{-1}) arsenic (As)-impacted populations, such as the development and progression of type-2 diabetes mellitus (T2DM), are often neglected given the primary emphasis of public health authorities on As carcinogenicity. We gathered studies reporting urinary biomarkers of As exposure (U-As) and biomarkers associated with T2DM and its complications (U-T2DM), such as renal damage, oxidation stress, low-grade inflammation, and endothelial damage. Studied U-T2DM biomarkers were: 8-hydroxy-2′deoxyguanosine, *N*-acetyl-β-D-glucosaminidase, β2-microglobulin, and albumin. Data was expressed as: either arithmetic means and standard deviations, or geometric means and geometric standard deviations, or correlation coefficients of U-As and U-T2DM. Urinary As concentrations were consistently associated with the aforementioned biomarkers of T2DM pathologic complications. Despite the limited selectivity of the selected T2DM biomarkers, a per unit change in As exposure level was reflected in the corresponding T2DM biomarker urinary concentrations. Our systematic review provides new evidence on the role of environmental As exposures influencing the T2DM disease process. Additional epidemiologic studies onto the association between As and T2DM should incorporate both urinary As and T2DM biomarkers, as suggested in this study, in order to evaluate subclinical effects of low-level As exposures.

Introduction

Type-2 diabetes mellitus (T2DM), one of the predominant chronic diseases, is currently affecting millions of people, reaching a global prevalence of 6.6% in 2010 for adults 20–79 years old (IDF, 2009). Chronic diseases, including T2DM, represent one of the most severe economic burdens impeding global development, slightly smaller in magnitude when compared with that of oil and gas price spikes and asset price collapse (IDF, 2009). Classic risk factors for T2DM including obesity, aging, physical inactivity, family history, and genetic polymorphism often fail to adequately explain the observed magnitude of incidence rates of T2DM (Navas-Acien et al., 2006, 2008). Greater than 90% of reported diabetic subjects suffer from non-insulin dependent T2DM; however, the exact etiology of type-2 T2DM, remains unclear (Campbell, 2009).

During the last decade, human exposures to environmental toxicants, such as arsenic (As), have been increasingly suspected with regard to T2DM development and progression (Navas-Acien et al., 2006, 2008). Arsenic-impacted areas are widespread, especially those characterized by low-level (<100 μg As L^{-1} water) As contamination of drinking water supplies. Public health interventions in low-level As-impacted populations typically focus on As carcinogenic effects, often neglecting to address non-carcinogenic effects, such as increased risk of T2DM. Higher As exposures (>500 μg As L^{-1} water) have been linked to increased T2DM incidence (Chen et al., 2007; Navas-Acien et al., 2006). T2DM prevalence was 2–5 times higher in arseniasis-endemic areas compared with non-endemic areas in Taiwan with an odds ratio (OR) and 95% CI of 10.05 (1.30–77.9) (Lai et al., 1994). Similar observations were made in studies conducted in other countries, such as Sweden, with an OR and 95% CI of 7.0 (0.7–79) (Rahman and Axelson, 1995), Mexico with an OR and 95% CI of 2.84 (1.64–4.92) (Coronado-Gonzalez et al., 2007) and Bangladesh with an OR and 95% CI of 5.2 (2.5–10.5) (Rahman et al., 1998). The above-mentioned studies reported associations between high levels of arsenic in drinking water and prevalence of T2DM. However, Navas-Acien et al. (2008) reported positive association between low to moderate exposure of arsenic via drinking water (<100 μg As L^{-1}), urinary As levels,

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and occurrence of T2DM (Navas-Acien et al., 2008). Recent work of our group at a low-level As exposed area of Cyprus showed that the OR for T2DM, comparing participants in the 80th versus the 20th percentiles of low-level As cumulative lifetime exposure index values, was 5.0 (1.03, 24.17), but after adjusting for age, smoking, education, and fish consumption, the As exposure effect on T2DM was not significant (Makris et al., 2012). Contrasting observations of no-association between As exposure and T2DM occurrence were reported in Chile and Argentina (Longnecker and Daniels, 2001) and Bangladesh (Chen et al., 2010). Hence, further studies are needed in order to gain a better understanding of the role of As exposure in the development and progression of T2DM.

Diabetes development is slow and symptoms may appear several years after onset of exposure (4–7 years) (Matheson et al., 2010; Waugh et al., 2007). Interestingly, a relatively high percent of T2DM (30–90%) remains undiagnosed (Wild et al., 2004), until a later stage when T2DM-related complications become more apparent. Early T2DM detection is of fundamental importance in public health policy and in the development of strategies to effectively reduce the associated morbidity. Remarkable efforts have been placed upon the development of biomarkers sensitive to the onset of T2DM and its complications (Matheson et al., 2010). Diabetes-related biomarkers have been identified in the literature (>100 published human studies, Table SI-1) based on three major pathological complications that are typically encountered prior to T2DM diagnosis: (i) renal damage, (ii) oxidative stress, and (iii) low-grade inflammation and endothelial damage. Based on their clinical relevance, urinary biomarkers, such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), *N*-acetyl-β-D-glucosaminidase (NAG), β2-microglobulin (β2MG), and albumin, are widely used for early T2DM diagnosis (Matheson et al., 2010). 8-Hydroxy-2′-deoxyguanosine is a common oxidative stress indicator, and albumin is widely used along with the oral glucose tolerance test for T2DM detection, while the other two urinary biomarkers (NAG and β2MG) are also used for T2DM detection (Matheson et al., 2010).

Currently, solid evidence is lacking to causally ascribe (low-level) As exposure to T2DM development and its complications, primarily due to differences in human-based study designs and interpretations (Navas-Acien et al., 2006). We hypothesized that exposure assessment studies in As-impacted populations could shed light on the possible onset of T2DM by looking at specific T2DM-related urinary biomarkers. Our objective was to delineate the degree of association between biomarkers of As exposure and those of T2DM-related pathological complications, such as renal damage, oxidative stress, low-grade inflammation, and endothelial damage.

Methods

A literature search from 1980 to 2011 was conducted using MEDLINE and ISI Web of Knowledge databases using the following inclusive criteria: (1) only human studies; (2) only adult data (>18 years old); (3) environmental As exposures (not occupational As exposures); (4) urinary biomarkers of As exposure; and (5) some urinary biomarkers of T2DM and its complications. The keywords used for database searching were "arsenic AND biomarker* AND urine", "arsenic AND urine AND water", "arsenic AND diabetes", "arsenic AND renal", "arsenic AND kidney", "diabetes AND biomarker* AND urine", and "arsenic AND diabetes AND biomarker*". Peer-reviewed manuscripts in English language were considered while conference abstracts and other information on the World Wide Web were excluded. In addition, the cited bibliography in each of the manuscripts of interest was thoroughly screened to obtain back referenced material relating to the topics of interest. Literature was also searched for studies measuring both biomarkers of As exposure and other T2DM-related biomarkers, such as transferrin, type IV collagen, fibronectin, retinol-binding protein, α1-microglobulin, pentosidine, and orosomucoid, but no studies were found.

Furthermore, a thorough review article on urinary biomarkers of T2DM was used for identifying articles that studied individual biomarkers of T2DM (Matheson et al., 2010). However, none of these studies looked into possible As exposure effects. On the other hand, a recent review article on the association of As and T2DM incidence rates (Navas-Acien et al., 2006) presented a table on the criteria used in such epidemiologic studies; out of 19 studies summarized in the Navas-Acien et al. (2006) review paper that reported arsenic association with T2DM, only two of them (Ward and Pim, 1984; Ruiz-Navarro et al., 1998) included urinary As measurements, but none of these reported on the relevant enzymatic biomarkers. In addition, a review article on As exposure biomarkers provided insight into oxidative stress and DNA damage (De Vizcaya-Ruiz et al., 2009). We selected four major urinary biomarkers being common to both As exposures and T2DM: 8-hydroxy-2′-deoxyguanosine (U-8OHdG), *N*-Acetyl-β-D-glucosaminidase (U-NAG), β2-microglobulin (U-β2MG), and albumin (U-albumin). Literature on the association of these urinary biomarkers to T2DM are presented in Table SI-1, with 9 references focusing on 8-OHdG, and 27, 14, 51 focusing on NAG, β2MG, and albumin, respectively (Table SI-1).

From the detailed search, we found 29 articles that measured urinary As and the four urinary T2DM biomarkers of interest – 13 studies measured 8-OHdG, 5 studies measured NAG, 6 studies measured β2MG, and 5 studies measured albumin. Ten of the thirteen 8-OHdG studies were included based on reported total As in drinking-water of the study locations, while three were excluded since only a cut-off limit value of $<50\ \mu g\ L^{-1}$ was given in Li et al. (2008), while no relevant information was presented in Wong et al. (2005) and Mori et al. (2011). The details of the selected studies are summarized in Table 1, while exclusion criteria for sixteen relevant studies are laid out in the supplementary section. Data in the form of an arithmetic mean (AM), or a geometric mean (GM), or a median, were extracted from the studies listed in Table 1. Pearson correlation coefficients were computed estimating the association of mean U-As and mean levels of T2DM-biomarkers using JMP software.

Each one of the groups studied was stratified into four broad categories, namely (control subjects, case subjects, total subjects, and low-level water As exposure subjects). The category of "control" subjects referred to healthy individuals that had not been exposed to As, whereas the remainder of the subjects were classified into the "case" subjects category. In general, control subjects had lower levels of the four T2DM related urinary biomarkers considered in comparison to the case subjects. All the subjects together were treated as the "total" subjects' category and the case subjects exposed to $<100\ \mu g\ L^{-1}$ As in drinking water were further classified into the low-level water As exposure subjects group. However, water-As data was only available in the studies measuring 8-OHdG biomarker (Table 1). Hence, based on all 8-OHdG studies presented in this report, an equivalent cut-off limit of $300\ \mu g\ g^{-1}$ urinary As concentration was established, corresponding to $<100\ \mu g\ L^{-1}$ water As concentrations. Based on this U-As level, studies and data on the other three biomarkers (U-NAG, U-b2MG, and U-albumin) were accordingly classified or not into the low-level water As exposure category.

We further calculated the log-transformed ratio of mean (RoM) defined as the ratio of the mean urinary T2DM biomarker concentration divided by its corresponding mean urinary As concentration in an attempt to evaluate the T2DM biomarker changes as a result of a per unit change in As exposure level. A Taylor series expansion