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REVIEW ARTICLE

Arsenic and diabetes: Current perspectives

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Abstract Arsenic is a naturally occurring toxic metalloid of global concern. Many studies have indicated a dose–response relationship between accumulative arsenic exposure and the prevalence of diabetes mellitus (DM) in arseniasis-endemic areas in Taiwan and Bangladesh, where arsenic exposure occurs through drinking water. Epidemiological researches have suggested that the characteristics of arsenic-induced DM observed in arseniasis-endemic areas in Taiwan and Mexico are similar to those of non-insulin-dependent DM (Type 2 DM). These studies analyzed the association between high and chronic exposure to inorganic arsenic in drinking water and the development of DM, but the effect of exposure to low to moderate levels of inorganic arsenic on the risk of DM is unclear. Navas-Acien et al. recently proposed that a positive association existed between total urine arsenic and the prevalence of Type 2 DM in people exposed to low to moderate levels of arsenic. However, the diabetogenic role played by arsenic is still debated upon. An increase in the prevalence of DM has been observed among residents of highly arsenic-contaminated areas, whereas the findings from community-based and occupational studies in low-arsenic-exposure areas have been inconsistent. Recently, a population-based cross-sectional study showed that the current findings did not support an association between arsenic exposure from drinking water at levels less than 300 μg/L and a significantly increased risk of DM. Moreover, although the precise mechanisms for the arsenic-induced diabetogenic effect are still largely undefined, recent *in vitro* experimental studies indicated that inorganic arsenic or its metabolites impair insulin-dependent glucose uptake or glucose-stimulated insulin secretion. Nevertheless, the dose, the form of arsenic used, and the experimental duration in the *in vivo* studies varied greatly, leading to conflicting

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results and ambiguous interpretation of these data with respect to human exposure to arsenic in the environment. Moreover, the experimental studies were limited to the use of arsenic concentrations much higher than those relevant to human exposure. Further prospective epidemiological studies might help to clarify this controversy. The issues about environmental exposure assessment and appropriate biomarkers should also be considered. Here, we focus on the review of mechanism studies and discuss the currently available evidence and conditions for the association between environmental arsenic exposure and the development of DM.

Introduction

Arsenic is a naturally occurring toxic metalloid of global concern. It can be found as inorganic and organic forms in the environment. Inorganic forms of arsenic, which are the predominant forms in surface and groundwater reservoirs, are more toxic than the organic forms. Arsenic can be easily solubilized in groundwaters, depending on pH, redox conditions, temperature, and solution composition. Many geothermal waters contain high concentrations of arsenic. Natural arsenic in groundwater at concentrations greater than the drinking water standard of 10 μg/L is not uncommon. Man-made sources of arsenic, such as mineral extraction and processing wastes, poultry and swine feed additives, pesticides, and highly soluble arsenic trioxide stockpiles, are also not uncommon and have contaminated soil and drinking water [1,2]. Arsenic-contaminated food is also a widespread problem worldwide [3]. It has been described that data derived from population-based studies, clinical case series, and case reports relating to ingestion of inorganic arsenic in drinking water, medication, or contaminated food or beverages show the capacity of arsenate and arsenite to adversely affect multiple organ systems [3]. An estimated 36 million people in the Bengal Delta are at risk because of the consumption of arsenic-contaminated water. The occurrence of arsenic contamination in groundwater in Taiwan has been recognized for several decades [1]. Epidemiological studies have demonstrated that it was associated with chronic exposure to arsenic in drinking water and increased rates of various chronic diseases, including cancers; diseases of the nervous system; peripheral vascular disease (blackfoot disease, a peripheral artery disease); and endocrine dysfunction in the United States and other countries [4,5]. Therefore, the United States Environmental Protection Agency recommended a reduction in the maximum contaminant level from 50 μg/L to 10 μg/L for arsenic in public drinking water supplies. In Taiwan, the areas along the southwestern coast are known to have arsenic contamination in drinking-water wells or undergroundwater, and hyperendemic occurrence of peripheral vascular disease (as blackfoot disease) is observed in the villages of these areas [5–7]. In these areas, arsenic concentrations in drinking water are measured and found to be in the range 0.35–1.14 mg/L, with a median concentration of 0.78 mg/L, in the early 1960s [8].

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion by pancreatic β-cells and/or insulin action on peripheral tissues. From the multivariable diabetes risk score, it has been analyzed that the number of adults at a high risk of diabetes was 38.4 million in 1991 and 49.9 million in 2001 in the United States [9]. The authors also predicted the total diabetes burden to be 11.5% (25.4 million) in 2011, 13.5% (32.6 million) in 2021, and 14.5% (37.7 million) in 2031 [9]. Insulin-dependent DM (IDDM or Type 1 DM) is caused by autoimmune or idiopathic destruction of the insulin-producing pancreatic β-cells, leading to a severe deficiency of insulin (hypoinsulinemia) and the elevation of blood glucose levels (hyperglycemia) [10]. Various proinflammatory cytokines, such as interleukin-1β, tumor necrosis factor α, interferon-γ, and reactive oxygen species, have been found to play important roles in islet β-cell destruction. A key role played by nuclear factor (NF)-κB signaling in cytokine-induced β-cell dysfunction and death was also shown [11,12]. In addition, non-insulin-dependent DM (NIDDM or Type 2 DM) is a multiorgan disease with an unknown specific etiology (although hereditary factors, aging, and obesity are important risk factors) that involves both peripheral insulin resistance in adipose, liver, and muscle cells, and insufficient insulin production because of pancreatic β-cell dysfunction [13]. It is estimated that approximately 90–95% of diabetes cases are Type 2 DM, whereas less than 10% of the cases are Type 1 DM and other specific types.

Many studies have indicated that there is a dose–response relationship between accumulative arsenic exposure and prevalence of DM in the villages along the south-western coast of Taiwan, where the inhabitants are exposed to arsenic through drinking water (0.1–15 mg/L and >15 mg/L every year). The incidence of DM in these villages was two to five times higher than that in other areas where arseniasis is non-endemic [14,15]. Moreover, similar studies have been reported in Bangladesh, Sweden, and the United States [16–18]. Therefore, chronic exposure to arsenic implies a risk factor for DM in the arsenic-contaminated environments. However, the detailed effects and molecular mechanisms of arsenic-related DM remain unclear.

Epidemiological research

Positive suggestions

In 1994, Lai et al. [14] first reported that chronic exposure to inorganic arsenic from drinking water may be associated with the prevalence of DM in the blackfoot disease–hyperendemic villages of Taiwan. The authors further suggested the presence of a dose–response relationship