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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

between cumulative arsenic exposure and the prevalence of DM; the multivariate-adjusted odds ratios were 6.61 and 10.05 for those who had cumulative arsenic exposures of 0.1–15.0 ppm/yr and greater than 15.0 ppm/yr, respectively, compared with those who were unexposed [14]. Other research showed a link between the prevalence of DM and the chronic consumption of groundwater, which contains high levels of inorganic arsenic, and this finding was later confirmed by several cross-sectional studies from Taiwan [7,19–21]. In Bangladesh, the crude prevalence ratio of DM among arsenic-exposed individuals with keratotic lesions was evaluated to be 4.4 (with a 95% confidence interval of 2.5–7.7) [17]. Nabi et al. [22] further found that the prevalence of DM among chronic arsenic-exposed individuals in Bangladesh, where the average levels of arsenic in the drinking water and spot urine samples were 218.1 ppb and 234.6 ppb, respectively, was approximately 2.8 times higher than that in the unexposed individuals. In case–control data from a Swedish copper smelter study, the odds ratios for DM with increasing arsenic exposure categories (<0.5 mg/m^3, 0.5 mg/m^3, and >0.5 mg/m^3) were found to be 2.0, 4.2, and 7.0 (the unstratified test for trend was weakly significant, $p = 0.03$), respectively [16]. In Mexico, a case–control study in an arseniasis-endemic region also found that subjects with intermediate total urinary arsenic levels (63.5–104 μg/g creatinine) were at a twofold higher risk of diabetes (odds ratio = 2.16; 95% confidence interval = 1.23–3.79), but the risk was almost three times greater in individuals with higher levels of total urinary arsenic (odds ratio = 2.84; 95% confidence interval = 1.64–4.92) [23]. Moreover, epidemiological researches have suggested that the characteristics of arsenic-induced DM in arseniasis-endemic areas in Taiwan and Mexico are similar to those of Type 2 DM [19–21,23]. These findings suggest that the ingestion of arsenic may predispose the development of DM in arsenic-endemic areas.

The aforementioned epidemiological studies analyzed the association between high chronic exposure to inorganic arsenic in drinking water and the development of DM. However, the effect of exposure to low to moderate levels of inorganic arsenic on the risk of DM is unclear. Recently, Navas-Acien et al. [24] reported that the odds ratio for Type 2 DM was 3.58 (95% confidence interval = 1.18–10.83), when they compared participants at the 80th percentile with those at the 20th percentile for the level of total urinary arsenic (16.5 μg As/L *vs.* 3.0 μg As/L). Therefore, the authors suggested a positive association between total urine arsenic, which reflected the inorganic arsenic exposure from drinking water and food, and the prevalence of Type 2 DM in people with low to moderate arsenic exposure.

The studies of Lai et al. [14] and Tsai et al. [7] have indicated an increased prevalence of diabetes in women compared with that in men occurred after 40 years of age in areas with high levels of inorganic arsenic in drinking water. For both men and women, the prevalence of DM increased with age. The prevalence was slightly higher among men than among women before 40 years of age. However, the prevalence was higher among women than among men thereafter (the age-adjusted prevalence was significantly higher in women), especially in the postmenopausal phase (>50 years of age, i.e. women who had low or deficient estrogen levels) in areas with high levels of arsenic in drinking water [7,14]. The study of Wang et al. [21] also showed that the prevalence odds ratios of diabetes in the arseniasis-endemic areas in Taiwan, in comparison with the non-endemic areas, were consistently greater for women than for men. It was also suggested that the association between arsenic exposure (in a blackfoot disease–endemic area) and DM was likely to be causal in women but not in men [25]. Chiou et al. [5] showed that the prevalence of microvascular diseases significantly increased with arsenic exposure, especially at higher levels, and that the relationship was stronger in diabetic than in nondiabetic subjects. For diabetic patients, the prevalence of microvascular diseases among female subjects was greater than that in male subjects for all categories of the arsenic levels [5].

Weak points and negative suggestions

Epidemiological and scientific results indicate that the diabetogenic role of arsenic is still debated upon. An increased 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 [15,26–28]. A case–reference analysis on the death records of Swedish art glass workers, who were regarded as potentially exposed to arsenic, showed a slightly elevated risk (Mantel–Haenszel odds ratio = 1.2, 95% confidence interval = 0.82–1.8) for DM. This study provided limited support for the possibility that occupational arsenic exposure could play a role in the development of DM [26]. The reviewed article by Tseng et al. [15] also stated that the use of weak cross-sectional or case–control study designs, the use of glucosuria or DM death as diagnostic criteria, and the lack of adjustment for possible confounding variables in some studies are major limitations that weaken the evidence for an association between arsenic exposure and DM in studies from Taiwan, Bangladesh, and Sweden [15]. Similarly, a systematic review by Navas-Acien et al. mentioned that the available evidence was inadequate to establish a causal role played by arsenic in DM. They suspected that methodological issues limited the interpretation of the association in the studies from Taiwan and Bangladesh, and the evidence from occupational studies and from the general populations in countries other than Taiwan or Bangladesh was inconsistent [27]. Chen et al. [28] also commented that the reason for inconsistent findings of arsenic and DM in occupational studies may be related to the "healthy worker effect" and the variation in exposure measurement; age composition; patient number; accuracy in diagnosis; and classification of underlying causes of death, competing causes of death, and DM detection methods. Moreover, the recent study by Kile and Christiani indicated that one of the limitations in the analysis of an association between arsenic exposure and DM has been the use of total urinary arsenic as the exposure metric. They further explained that the use of urinary arsenic as a biomarker may cause difficulty in ascertaining historical exposures that may be more relevant for the pathogenesis of Type 2 DM, because urinary arsenic is a biomarker of

short-term exposure with a half-life of approximately 3 days [29].

There have been no reports concerning DM in populations known to be exposed to high levels of arsenic in drinking water in Chile and Argentina, although this could reflect a lack of research or be related to a publication bias [30]. Recently, Chen et al. conducted a population-based cross-sectional study using baseline data of 11,319 participants in Bangladesh to evaluate the association between well water arsenic and total urinary arsenic concentration and the prevalence of DM and glucosuria. The authors found that more than 90% of the cohort members were exposed to drinking water with an arsenic concentration less than 300 μg/L and observed no association between arsenic exposure and the prevalence of DM and glucosuria: there is no evidence of an association between well water arsenic concentration, total urinary arsenic, or the composition of urinary arsenic metabolites and glycosylated hemoglobin (HbA1c) levels [31].

Basic research

In vitro experimental studies

Insulin, a metabolic hormone produced and secreted by the pancreatic islet β-cells, triggers the principal responses to lower blood glucose level by stimulating the uptake of glucose into skeletal muscle and peripheral adipose tissue as well as suppressing gluconeogenesis and glycogenolysis in the liver. Insulin insufficiency causes deleterious effects on glucose homeostasis, involved in the pathophysiological processes of Type 1 and 2 DM [32]. Physiologically, glucose transport into the pancreatic β-cells could induce insulin secretion. The signal transduction pathway begins with the entrance of glucose into the cell through a transporter followed by glycolysis and leads to the production of adenosine triphosphate, which, in turn, closes the adenosine triphosphate-sensitive potassium channel and depolarizes and opens the voltage-dependent calcium channel present in the cell membrane. A calcium flux through the opened channels finally triggers exocytosis of insulin from the β-cells [33,34]. On the other hand, oxidative stress is induced under diabetic conditions through various pathways, including the electron transport chain in mitochondria and the nonenzymatic glycosylation reaction, and is likely to be involved in the progression of the pancreatic β-cell dysfunction that develops in DM [11]. Pancreatic β-cells are the most vulnerable to oxidative stress-induced damage because they have lower levels of antioxidant enzymes, such as glutathione peroxidase, superoxide dismutase, and catalase [35]. Superoxide has been suggested to impair glucose-stimulated insulin secretion in pancreatic β-cells in which endogenous superoxide was released from the mitochondria [36]. If excess oxidative stress is produced in the pancreatic β-cells, it may be expected to impair insulin secretion.

Although the cellular and molecular mechanisms by which arsenic induces its diabetogenic effect are still largely undefined, recent *in vitro* experimental studies indicate that inorganic arsenic or its metabolites impair insulin-dependent glucose uptake or glucose-stimulated insulin secretion. Table 1 presents several *in vitro* studies regarding the effects of arsenic on insulin-dependent glucose uptake or glucose-stimulated insulin secretion, published in the past 5 years. The study by Diaz-Villasenor et al. [37] showed that the incubation of isolated rat pancreatic islets with a subtoxic concentration of arsenite (5 μM) for 72 hours significantly inhibited glucose-stimulated insulin secretion and mRNA expression. Diaz-Villasenor et al. further demonstrated that subchronic low levels of arsenite (0.5–2 μM) impaired insulin secretion by decreasing the oscillation of intracellular free Ca^{2+}, thus reducing calcium-dependent calpain-10 partial proteolysis of the synaptosomal-associated protein of 25 kDa (a member of the insulin secretory machinery) [38]. Yen et al. [39] also showed that arsenic trioxide (As_2O_3, 1–10 μM) induced the dysfunction of insulin secretion, which may be mediated by oxidative stress in pancreatic β-cells. Interestingly, a recent study by Fu et al. [40] showed that the exposure of pancreatic β-cells to low levels of arsenite (0.05–0.5 μM) impaired glucose-stimulated insulin secretion. The authors further suggested that nuclear factor-erythroid 2-related factor 2 activation and the induction of antioxidant enzymes in response to arsenic exposure impede reactive oxygen species signaling involved in glucose-stimulated insulin secretion and thus disturbed β-cell function [40]. These findings suggested that arsenic contributes to the development of DM by impairing pancreatic β-cell functions, particularly insulin synthesis and secretion.

Insulin-stimulated glucose uptake by peripheral tissues is a crucial process responsible for the regulation of postprandial blood glucose levels. Disruption of glucose homeostasis can involve impaired glucose utilization and/or insulin resistance by adipose tissue and skeletal muscle [50]. It has been indicated that arsenicals can alter signal transduction factors, including p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K) and its downstream signals 3-phosphoinositide-dependent kinase-1 and PI3K-dependent phosphorylation of protein kinase B (PKB/Akt), tumor necrosis factor-α, interleukin-6, and NFκB, to affect insulin-stimulated glucose uptake in adipocytes or skeletal muscle cells [51,52]. Disruption of insulin-stimulated glucose uptake has been suggested to be the response to chronic arsenic exposure for potential mechanism to develop the Type 2 DM. Phenylarsine oxide, an aromatic derivative of trivalent arsenic, has been shown to inhibit insulin-stimulated glucose transport in adipocytes, which may be associated with the inhibition of phosphorylation of endogenous phosphoproteins (p24 and p240) [53–55]. Later reports demonstrated that phenylarsine oxide inhibits the insulin-stimulated glucose transporter (GLUT)4 translocation and triggers GLUT4 degradation in adipocytes [56,57]. Moreover, the recent study by Scott et al. [41] found that phenylarsine oxide stimulates glucose uptake at low concentrations (3 μM, 30 minutes) but inhibits glucose uptake at a higher concentration (40 μM) in L929 mouse fibroblast cells, which express only GLUT1. On the other hand, insulin-stimulated p38 MAPK phosphorylation has been shown to increase GLUT4 translocation, resulting in an increase in glucose uptake [58,59]. Akt (PKB) signaling expression is also one of the key steps in the activation of GLUT4 and its translocation to the cellular membrane in response to insulin [60,61]. Several studies have found that

Table 1 Arsenic: *in vitro* and *in vivo* experiments

Main references	Experimental cells/animals	Arsenic exposure	Exposure dose and duration	Results
In vitro experiments				
[37]	Isolated islets	Arsenite	0.5—10 μM, 72 hr or 144 hr	GSIS (5 μM, 72 hr) ↓ Insulin mRNA levels ↓
[38]	β-Cells	Arsenite	0.5—2 μM, 72 hr	GSIS ↓ Intracellular free $[Ca^{2+}]i$ ↓ SNAP-25 proteolysis ↓
[39]	β-Cells	Arsenic trioxide (As_2O_3)	1—10 μM, 2—8 hr	Insulin secretion ↓ ROS generation ↑ ATP depletion and cell apoptosis GSIS ↓ Nrf2 activity ↑
[40]	β-Cells	Arsenite	0.05—0.5 μM, 96 hr	Intracellular GSH ↑ Glucose-stimulated intracellular peroxide production ↓
[41]	Fibroblasts	PAO	1—40 μM, 30 min	Glucose uptake at low-dose PAO ↑ Glucose uptake at high-dose PAO ↓
[42]	Adipocytes	Arsenite MAs^{III}	50 μM, 4 hr 2 μM, 4 hr	ISGU ↓ PDK-1 and Akt phosphorylation ↓
[43]	Myoblasts	Arsenic trioxide	0.1—0.5 μM	Inhibition of myogenesis Akt phosphorylation ↓
[44]	Wistar rat (♂)	Arsenite (ip)	5.55 ppm, 30 d	Blood glucose levels ↑ Liver glycogen ↓
[45]	Wistar rat (♂)	Arsenite (og)	1.7 mg/kg, 90 d	Blood glucose levels ↑ Plasma insulin levels ↑ HOMA-IR index ↑ Low insulin sensitivity
[46]	C57BL/6 mice (♂)	Arsenite (po)	10 ppb, 50 ppb, 21 d	Altered hexokinase II expression
[47]	C57BL/6 mice (♂)	Arsenite (po)	25 ppm, 50 ppm, 56 d	Impaired glucose tolerance
[48]	C57BL/6 mice (♂)	Arsenite (po)	1—50 ppm, 8 wk	Impaired glucose tolerance
[39]	ICR mice (♂)	Arsenic trioxide (po) (As_2O_3)	10 ppm, 5—12 wk	Decreased plasma insulin
[49]	LM/Bc/Fnn mice (♀)	Arsenate (ip)	9.6 mg/kg, 2 d	Fasting plasma glucose ↑ Fasting plasma insulin ↑ HOMA-IR index ↑ Impaired glucose tolerance

↑ = increase; ↓ = decrease; ATP = adenosine triphosphate; GSH = glutathione; GSIS = glucose-stimulated insulin secretion; HOMA-IR = homeostasis model assessment of insulin resistance; ip = intraperitoneal; ISGU = insulin-stimulated glucose uptake; MAs^{III} = methylarsonous acid; Nrf2 = nuclear factor-erythroid 2-related factor 2; og = oral gavage; PAO = phenylarsine oxide; PDK-1 = 1,3-phosphoinositide dependent kinase 1; po = per oral in drinking water; ROS = reactive oxygen species; SNAP-25 = synaptosomal-associated protein of 25 kDa.

exposure to high levels of arsenicals (phenylarsine oxide or arsenite) can stimulate basal glucose uptake (insulin independent) in adipocytes and skeletal muscle cells [62—65]. These effects of toxic concentrations of arsenicals were associated with the activation of p38 MAPK or PI3K/Akt-mediated signal pathways [62,63,65—67]. A study by Paul et al. [42] demonstrated that short-term exposure to arsenite and methylarsonous acid significantly inhibited insulin-stimulated glucose uptake in adipocytes through a 3-phosphoinositide-dependent kinase-1/PKB/Akt-mediated transduction pathway. Yen et al. [43] also found that low doses of arsenic (As_2O_3, 0.1—0.5 μM) inhibited myogenic differentiation and muscle regeneration through a PKB/Akt-related signaling pathway. These findings suggested that arsenic contributes to the development of DM or insulin resistance by impairing insulin-stimulated glucose uptake.

In vivo experimental studies

Previous studies have investigated the alterations of blood glucose and insulin levels in goats, rats, and mice treated with arsenite or arsenate by means of food, drinking water, or intraperitoneal injection [68—72]. However, the dose, form of arsenic used, and the experimental duration in these studies varied greatly, leading to conflicting results and ambiguous interpretation of the data with respect to human exposure to arsenic present in the environment. Table 2 shows the potential responses for diabetogenic effect associated with chronic exposure to arsenic in animals published in the past 5 years. These studies examined blood glucose or insulin levels in rats or mice after exposure to inorganic arsenic through drinking water, oral gavage, or intraperitoneal injection. Blood glucose and

Table 2 Arsenic: epidemiological research

Main Refs.	Suggestions	Location and As exposures	Results
[14]	Positive	Taiwan: drinking-water As, 0.1–15 ppm/yr or >15 ppm/yr	A dose–response relationship between cumulative As exposure and the prevalence of DM
[22]	Positive	Bangladesh: drinking water—average As, 218.1 ppb; spot urine—average As, 234.6 ppb	The prevalence of DM among chronic As-exposed subjects was approximately 2.8 times higher than that in the unexposed subjects
[23]	Positive	Mexico: urinary As, 63.5–104 μg/g creatinine	Twofold higher risk of DM
[16]	Positive	Sweden: occupational As (copper smelter)—<0.5 mg/m^3, 0.5 mg/m^3, and >0.5 mg/m^3	The odds ratios for DM with increasing As exposure categories were 2.0, 4.2, and 7.0, respectively
[24]	Positive	USA: median urine total As, 7.1 ppb	The prevalence of Type 2 DM was 7.7%.
[26]	Negative	Sweden: occupational As exposure (art glass workers)	Limited support for As exposure plays a role in the development of DM
[31]	Negative	Bangladesh: drinking water, <300 ppb	No association between As exposure and the prevalence of DM and glucosuria

As = arsenic; DM = diabetes mellitus.

liver glycogen level were decreased in rats exposed to 5.55 ppm arsenite by intraperitoneal injection for 30 consecutive days [44,73]. Izuierdo-Vega et al. [45] found that hyperglycemia, hyperinsulinemia, low insulin sensitivity, elevated homeostasis model assessment of insulin resistance, and increased pancreatic lipid peroxidation were induced by oral administration of sodium arsenite to rats at 1.7 mg/kg for 90 days. The authors also suggested that subchronic exposure to inorganic arsenic induced oxidative stress and oxidative damage in the pancreas, and this could be implicated as a cause of insulin resistance [45]. Moreover, the expression of hexokinase II in the renal cortical glomeruli was significantly upregulated in C57BL/6 mice exposed to low levels of arsenic (10 ppb and 50 ppb) through the drinking water for 21 days; altered hexokinase II expression in the renal cortex has been demonstrated to be associated with a variety of pathological conditions, including DM [46]. An impaired glucose tolerance was also observed in C57BL/6 mice exposed to a high level of arsenite (50 ppm) for 8 weeks; the authors further suggested that mice are less susceptible than humans to the arsenic-induced diabetogenic effect because of their ability to more efficiently clear arsenic or its metabolites from target tissues [47,48]. Yen et al. [39] reported that plasma insulin levels were significantly decreased in ICR mice exposed to arsenic trioxide (10 ppm) in drinking water for 5–12 weeks. Recently, Hill et al. [49] showed that arsenate (9.6 mg/kg), which was administrated by intraperitoneal injection to maternal LM/Bc/Fnn mice on gestational Days 7.5 and 8.5, significantly increased fasting plasma glucose and insulin levels, glucose intolerance, and homeostasis model assessment of insulin resistance.

Limitations and conclusions

Many epidemiological studies have indicated that exposure to arsenic from drinking water in arsenic-contaminated areas can induce DM, suggesting a possible role played by high levels arsenic exposure in DM, whereas the effects of exposure to lower concentrations of arsenic on diabetes are unclear (Table 2). A recent study by Navas-Acien et al. [24] found a positive association between total urinary arsenic and the prevalence of Type 2 DM in a population in the United States exposed to moderate levels of arsenic. The authors further indicated that the issue of involvement of arsenic in diabetes epidemic is a public health research priority with potential implications for the prevention and control of DM. Therefore, the environmental factors may play an important role in DM development and prevention.

On the other hand, the detection of urinary arsenic has been questioned to be not an appropriate biomarker to ascertain historical exposures for the pathogenesis of Type 2 DM [29]. Moreover, the recent findings by Chen et al. [31] did not support an association between arsenic exposure through drinking water at levels less than 300 μg/L and a significantly increased risk of DM. Therefore, further prospective epidemiological studies may help to clarify the controversy. The issues about environmental exposure assessment and appropriate biomarkers should also be considered.

The experimental studies were limited to the use of arsenic concentrations much higher than those relevant to human exposure. The current United States Environmental Protection Agency–recommended standard for arsenic in drinking water is 10 ppb. The concentration range of inorganic arsenic (arsenite) used in studies of glucose uptake in cultured cells was 400–750,000 ppb and that of arsenite in *in vivo* studies of glucose metabolism was 5,000–100,000 ppb [27]. Nevertheless, several recent studies used low levels of arsenic in the *in vitro* (0.05–0.5 μM) and *in vivo* (10 ppb and 50 ppb) experiments (Table 1). Moreover, whether arsenic through the generation of oxidative stress causes β-cell dysfunction and glucose metabolism/homeostasis, and whether chronic arsenic exposure affects the expression of the β-cell-related or glucose metabolism/homeostasis-related signaling transduction molecules and then alters blood glucose regulation and induces diabetes

are unknown. These doubts, therefore, also need to be clarified. Taken together, although the data from some laboratory studies support the incidence and clinical symptoms of arsenic-induced DM, many experimental data are presented insufficiently and inadequately to explain the epidemiological findings. It is important to identify the appropriate cell and animal models that can mimic human-exposed conditions in arsenic-contaminated areas, and thus can clearly link arsenic exposure and DM.

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