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Epidemiologic evidence of diabetogenic effect of arsenic

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Abstract

It is well documented that arsenic can lead to skin lesions, atherosclerotic diseases and cancers. The association between arsenic exposure and diabetes mellitus is a relatively new finding. Up to now, there are six epidemiologic reports linking diabetes mellitus with arsenic exposure from environmental and occupational sources. Two reports in Taiwan carried out in the blackfoot disease-hyperendemic villages, one cross-sectional and one prospective follow-up of the same cohort, indicate that arsenic exposure from drinking artesian well water is associated with prevalence and incidence of diabetes mellitus in a dose-responsive pattern. The observation of the relation between arsenic exposure and diabetes mellitus is further supported by studies carried out in Sweden and Bangladesh. In Sweden, case-control analyses of death records of copper smelters and glass workers revealed a trend of increasing diabetes mellitus with increasing arsenic exposure from inhalation. In Bangladesh, prevalence of diabetes mellitus among arsenic-exposed subjects with keratosis was about five times higher than unexposed subjects. Increasing trends of diabetes mellitus with indices of arsenic exposure in drinking water seems to be independent of the presence of skin lesions associated with arsenic exposure. Although these studies consistently show an association between arsenic exposure and diabetes mellitus, the weak study designs of cross-sectional or case-control, the use of glucosuria or diabetes death as diagnostic criteria and the lack of adjustment for possible confounders in some studies, are major limitations that may reduce the strength of the evidence.

Keywords: Epidemiology; Diabetes mellitus; Arsenic; Water pollutant; Occupational exposure

1. Introduction

Diabetes mellitus is a heterogeneous syndrome characterized by elevated blood glucose level. Most of the causes of diabetes mellitus are still unknown. However, impaired insulin secretion from the pancreas or impaired insulin action as a

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result of insulin resistance in the skeletal muscle, liver and adipose tissue have been noted in the diabetic patients (DeFronzo et al., 1997). Genetic predisposition and environmental factors are important in the development of diabetes mellitus. Family history, some ethnic groups, aging, physical inactivity, stress of life, intake of excessive calories, obesity, some viral infections, medications and chemicals are well-documented risk factors (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2001).

Some trace elements have been found to play influencing roles on the homeostasis of plasma glucose in human beings. For example, chronic iron overload can be toxic and causes diabetes mellitus (Kang, 2001) and deficiency of chromium can be associated with increased risk of diabetes (Anderson, 2000). On the other hand, chromium supplementation (Anderson, 2000) and vanadium administration (Cam et al., 2000) can improve insulin action and help to lower plasma glucose in patients with diabetes mellitus.

Arsenic is a ubiquitous element, which exists as the 20th most abundant element in the earth's crust. It can be found as organic or inorganic chemicals in the earth, the air, the water, or the living beings on earth. Human beings can be exposed to arsenic from the environment, medications, industrial pollution, mining, coal burning or food (Chen and Lin, 1994). Inorganic forms of arsenic are more toxic than the organic forms. In the history of human beings, arsenic intoxication causing health hazards has been noted for a few centuries. Nowadays, chronic arsenic intoxication is still a major health problem in some regions of some countries, especially those in Asia (Tseng, 1999). Atherosclerosis and cancers of the skin, lung, bladder, and liver have been well documented to be associated with long-term arsenic exposure (Chen and Lin, 1994). However, diabetes mellitus has only been recently found to be associated with arsenic exposure in some epidemiologic studies. A recent review by the Task Group meeting of the International Programme on Chemical Safety shows suggestive link between arsenic exposure and diabetes mellitus (The World Health Organization, 2001). After that review, a further study reporting an association between arsenic exposure from drinking water and diabetes mellitus based on a prospective follow-up study design was published (Tseng et al., 2000a,b). In the present paper, the authors aimed at reviewing the current available reports on the association between arsenic exposure and diabetes mellitus from the literature.

1.1. Taiwanese studies

The association between arsenic exposure and diabetes mellitus was first noted by Lai et al. (1994), who analyzed the data of 891 residents participating in a health examination in 1989 in an area characterized by arsenic exposure from drinking well water in the blackfoot disease hyperendemic villages along the southwestern coast of Taiwan. The diagnosis of diabetes mellitus was based on (1) a fasting glucose level of 7.8 mmol/l or greater and/or a 2-h glucose level of 11.1 mmol/l or greater after a 75 g oral glucose loading, or (2) a history of diabetes mellitus, for which the subjects were currently receiving treatments with insulin and/or oral antidiabetic agents. The prevalence of diabetes mellitus in these arseniasis-hyperendemic villages was found to be two times higher than the general population of Taiwan and a dose–response relation between cumulative arsenic exposure (CAE) and the prevalence of diabetes mellitus was demonstrated after adjustment for multiple risk factors. The multivariate-adjusted odds ratios were 6.61 (0.86–51.0) and 10.05 (1.30–77.9) for those with CAE of 0.1–15.0 and $\geq$15.1 mg/l years, respectively, while compared with the unexposed.

Tseng et al. (2000b) followed the same cohort without diabetes mellitus at the beginning in these arseniasis-hyperendemic villages with biannual oral glucose tolerance test up to 1993, and compared the incidence of diabetes mellitus with two non-endemic townships in Taiwan. The diagnosis of diabetes mellitus was similar with the study by Lai et al. (1994). During a follow-up period of 1499.5 person-years in 446 subjects in the arseniasis-hyperendemic villages, a total of 41 newly diagnosed cases of diabetes mellitus developed. The crude incidence of diabetes mellitus was 27.4 per 1000 person-years in the arseniasis-hyperen-

demic villages, while those reported in the non-endemic townships by Wang et al. were 9.0 and 9.8 per 1000 person-years in women and in men, respectively (Wang et al., 1997). After age-standardization to the US population in 1970, the incidence rate was 18.2 per 1000 person-years in the arseniasis-hyperendemic villages, which is about two times higher than the standardized rate of 9.3 per 1000 person-years in the non-endemic townships. The age-specific incidences of diabetes mellitus in the arseniasis-hyperendemic villages are also higher than the non-endemic townships with incidence density ratios of 3.55 (3.51–3.60), 2.32 (1.10–4.90), 4.31 (2.41–7.67) and 5.48 (2.23–13.45), respectively, for the age groups of 35–44, 45–54, 55–64 and 65–74 years. The incidences rose abruptly in the age groups above 55 years among villagers in arseniasis-hyperendemic area. These birth cohorts also have an abrupt increase in the prevalence of peripheral vascular disease assessed with Doppler ultrasonography (Tseng et al., 1994, 1995, 1996, 1997). They had a higher long-term arsenic exposure than those aged below 55 years. Their exposure history to well water was more than 30 years, which was deemed as an induction period for BFD, before the coverage of tap water supply became high. Tseng et al. (2000a) recently reviewed the available reports on the incidence of diabetes mellitus in Taiwan and have found that the incidence in the arseniasis-hyperendemic villages is the highest when compared with studies carried out in non-endemic areas in Taiwan. The incidence of diabetes mellitus in the arseniasis-hyperendemic villages in Taiwan was not only significantly higher than the non-endemic areas (external control), Tseng et al. (2000b) also demonstrated higher incidence rate in the higher arsenic exposure subgroup than the lower exposure subgroup (internal control) in the arseniasis-hyperendemic villages. Those with a CAE ≥ 17 mg/l years (median value among the incident cases) had a two times higher risk of developing diabetes mellitus after adjustment for age, sex and body mass index. When used as a continuous variable, CAE was associated with incidence of diabetes mellitus with a relative risk of 1.03 for every 1 mg/l year of exposure after multivariate adjustment ($P < 0.05$). Thus, a CAE difference of 50 mg/l years will result in an estimated relative risk of 4.4.

1.2. Swedish studies

With the epidemiologic evidence linking diabetes mellitus and arsenic exposure from drinking water observed in Taiwan, Rahman and Axelson (1995) retrospectively analyzed the risk of dying from diabetes mellitus in a case-control study carried out in copper smelter workers by comparing three arsenic exposure categories with an unexposed group from the records of male deaths for the years 1960–1976 in the parish register. Among 12 cases of diabetes, ten showed evidence of arsenic exposure; while among 31 controls, 17 had a history of arsenic exposure. An estimated odds ratio (95% CI) of 4.1 (0.6–33) was observed. When exposure was categorized into three subgroups of arsenic in the air of < 0.5, 0.5 and > 0.5 mg/m^3, the respective odds ratios were 2.0, 4.2 and 7.0, while compared with the unexposed control group. Although the 95% CI included unity for all exposure categories, a significant trend for risk of diabetes mellitus was observed in the three different categories of exposure ($P = 0.03$).

In another similar but larger study carried out among art glass workers during the period of 1950–1982, the odds ratios of dying from diabetes mellitus were similar for glass workers unlikely exposed to arsenic (i.e. grinders, engravers and similar workers, etchers, polishers, painters and similar workers, controllers, packers and similar workers) and an external population who were not glass workers. However, glass workers likely exposed to arsenic (i.e. glassblowers, other foundry workers and unspecified workers) had a slightly higher odds ratio of 1.4 (0.9–2.1) while compared with the external population. If the control group includes the unexposed glass workers and non-glass workers, the odds ratio for diabetic death in the exposed glass worker was 1.4 (0.92–2.2). Among the exposed workers, the unspecified glass workers, considered as having higher arsenic exposure, had a significantly higher risk of diabetes mellitus with odds ratio of 1.8 (1.1–2.8) when compared with the referent group (Rahman et al., 1996).

1.3. Bangladeshi study

In Bangladesh, a population of some 30–70 million people living in 41 districts out of the 64 are probably exposed to arsenic from drinking water (Rahman et al., 1999). The exposure probably started in late 1960s when drilling of tubewells began as part of a wide irrigation plan (Bagla and Kaiser, 1996). Typical skin lesions of arsenic exposure characterized by keratosis, hyperpigmentation and hypopigmentation have been noted in the exposed population.

Rahman et al. (1998) analyzed the prevalence rates of diabetes mellitus among 163 subjects with keratosis (taken as an indicator of exposure to arsenic) recruited from six districts with arsenic-contaminated drinking water and 854 unexposed subjects living in four suburbs of Dhaka without problems of arsenic contamination in Bangladesh. The diagnosis of diabetes mellitus was based on a positive history of diabetes mellitus during questionnaire interview or a stepwise examination of glucosuria followed by blood glucose test if the subjects showed suspected symptoms of diabetes. They have found that the prevalence ratio of diabetes mellitus for those with keratosis over the unexposed subjects is 5.2 (2.5–10.5) after adjustment for age, sex and body mass index. When a time-weighted mean arsenic exposure was used as an index of exposure dosage, a dose–response relation between exposure dosage and prevalence of diabetes mellitus was also demonstrated in this study. For those with levels of < 0.5, 0.5–1.0 and > 1.0 mg/l, the corresponding prevalence ratios were 2.6 (1.2–5.7), 3.9 (1.8–8.2) and 8.8 (2.7–28.4), while compared with the unexposed subjects. The trend in risk was statistically significant ($P < 0.001$).

In another study, Rahman et al. (1999) further examined the relation between arsenic exposure and glucosuria (taken as a proxy for diabetes mellitus) in subjects with and without skin lesions in Bangladesh by using both a time-weighted average concentration (mg/l) and mg years/l as exposure indices to arsenic. A significant dose–response relation between exposure to arsenic and glucosuria was observed for both indices in subjects with or without skin lesions. However, higher risk estimates were noted in those subjects with skin lesions. The respective prevalence ratios for those with skin lesions in the categories of arsenic exposure of < 1.0, 1.0–5.0, > 5.0–10.0 and > 10.0 mg years/l were 0.8 (0.3–1.9), 1.7 (0.9–2.9), 2.1 (1.0–4.0), and 2.9 (1.6–5.2) ($P < 0.001$).

2. Discussion and conclusion

The study by Lai et al. (1994) carried out in BFD area in Taiwan is the first cross-sectional epidemiologic study indicating an association between arsenic exposure from drinking water to diabetes mellitus. The method used to diagnose diabetes mellitus is classical and followed the criteria of the World Health Organization (WHO). The dose–response relation between arsenic exposure and the prevalence of diabetes mellitus is persuasive after adjusting for possible confounders. However, the temporality of cause and effect is not well clarified by a cross-sectional study.

The two studies done by Rahman et al. in the copper smelters (Rahman and Axelson, 1995) and the glass workers (Rahman et al., 1996) are retrospective, and case-control in design. Both of these studies used mortality data for analyses and the diagnosis of diabetes mellitus was based on the records of the death certificates. The number of the study subjects in the copper smelters was too small and the assessment of arsenic exposure in the glass workers was not very precise. Furthermore, because both of these two studies are retrospective and they referred to data file of more than 10 years old, no information on other possible confounders could be obtained. Despite these inherent limitations, a dose–response relation between arsenic exposure and diabetes mellitus could still be demonstrated in these two studies. They also provide some support for the hypothesis that arsenic is diabetogenic as proposed by Lai et al. (1994). These two studies give substantial implication that arsenic exposure from sources other than drinking water could also lead to diabetes mellitus. However, mortality study also suffers from the weakness that a cause of diabetes

death would not be recorded in the death certificate if the patients with diabetes mellitus die. Although excess mortality from diabetes could also be shown among the arsenic exposed population in an ecological study in Taiwan (Tsai et al., 1999), no significant excess mortality from diabetes was observed in the Utah study in the USA (Lewis et al., 1999).

The studies carried out in Bangladesh are more recent. The first report in 1998 (Rahman et al., 1998) demonstrated a higher risk for diabetes mellitus in a group of 163 subjects with keratosis (used as an indicator of arsenic exposure) while compared with 854 external controls without exposure. A significant trend for increased risk of diabetes mellitus was observed for increasing dosage of arsenic exposure. The second report in 1999 (Rahman et al., 1999) also demonstrated a dose–response relation between two indices of arsenic exposure and glucosuria (used as a proxy for diabetes mellitus) either in the absence or presence of keratosis. The second study suggests that the effect of arsenic on the development of diabetes mellitus is somehow independent of skin lesions such as keratosis. The methods used for diagnosis of diabetes mellitus in these two Bangladeshi studies were not similar and they were not based on the WHO criteria. Glucosuria is also a weak surrogate diagnostic method for diabetes mellitus.

The latest published paper by Tseng et al. (2000b) was the first prospective follow-up study. It was well demonstrated that arsenic exposure from the artesian well water has a dose–response relation with the incidence of diabetes mellitus among residents in the blackfoot disease-hyperendemic villages in Taiwan. An external control was also used for comparison and the incidence density ratios between endemic and non-endemic areas ranged from 2.32 to 5.48 for different age groups. The method used for diagnosis of diabetes mellitus followed the criteria of the WHO and the CAE index took into account the individual exposure. Age, sex and body mass index were also considered as possible confounders. The use of a prospective follow-up study design in this study is robust and provides a better clarification of the correctness of temporality in cause and effect.

Skin lesions and the atherogenic and carcinogenic effect of arsenic have long been observed in people exposed to arsenic (Chen and Lin, 1994). However, the association between arsenic exposure and diabetes mellitus has only been noted recently. The hypothesis of diabetogenic effect of arsenic as initiated by Lai et al. (1994) was supported by all the other later studies carried out in different ethnic groups with different sources of exposure (Rahman and Axelson, 1995; Rahman et al., 1996, 1998, 1999; Tseng et al., 2000b). To the best of our knowledge, there are six epidemiologic studies aiming at exploring the link between arsenic exposure and diabetes mellitus (Table 1). The sources of exposure are environmental and occupational. Although a positive association has been consistently observed in different ethnic groups, the use of weak study designs such as cross-sectional and case-control in some studies, the use of different methods for diagnosis of diabetes mellitus (for example, while some studies used the classical WHO criteria, others used weak indicators for diabetes mellitus such as glucosuria or diabetes death recorded on death certificate) and the lack of adjustment for possible confounders for diabetes mellitus in some studies are the limitations that may reduce the strength for this association. However, the correctness of temporality in cause-effect assessment was solved by the latest incidence study by Tseng et al., which also used a more robust study design of prospective follow-up study, followed the WHO diagnostic criteria and adjusted for possible confounders of age, sex and body mass index (Tseng et al., 2000b).

The arsenic-associated type of diabetes mellitus was probably non-insulin-dependent diabetes mellitus (or Type 2 diabetes mellitus) clinically, because almost all of the study subjects included were above 30 years of age and the clinical diagnosis of diabetes mellitus as described by all of the studies favored such a clinical type of disease. This type of diabetes mellitus as related to arsenic exposure is mostly clear as demonstrated by the study of Tseng et al. (2000b), because none of the incident cases of diabetes mellitus developed diabetic ketoacidosis or required insulin treatment during the period of follow-up. Moreover, all of

Table 1
Epidemiologic studies linking arsenic exposure and diabetes mellitus

Authors	Study design	Location	Source of arsenic exposure	Diagnosis of diabetes mellitus	Main findings
Lai et al. (1994)	Cross-sectional, 891 residents of blackfoot disease area	Taiwan, blackfoot disease endemic areas	Environment: Artesian well water	Oral glucose tolerance test	Prevalence of diabetes mellitus was associated with CAE. Multivariate-adjusted odds ratios (95% CI): 6.6 (0.9–51.0) and 10.1 (1.3–77.9) for CAE of 0.1–15.0 and >15.0 mg/l years, comparing with unexposed
Tseng et al. (2000a,b)	Prospective follow-up, 446 non-diabetic residents of blackfoot disease area were followed up to 4 years	Taiwan, blackfoot disease endemic areas	Environment: Artesian well water	Oral glucose tolerance test	Age-specific incidence density ratios were two to five times higher than non-endemic townships. For residents of blackfoot disease areas, relative risk was 2.1 (1.1–4.2) for CAE $\geq$17 mg/l years (median) versus a lower value
Rahman and Axelson (1995)	Retrospective, case-control, 12 cases with diabetes mellitus on death certificates and 31 controls	Sweden	Occupation: Copper smelter	Diabetes as a cause of death	Odds ratios for diabetes death were 2.0 (0.1–27), 4.2 (0.3–54) and 7.0 (0.7–79) for arsenic exposure in the air of <0.5, 0.5 and >0.5 mg/m^3 (test for trend, $P = 0.03$)
Rahman et al. (1996)	Retrospective, case-control, 240 cases with diabetes mellitus on death certificates and 2216 controls	Sweden	Occupation: Art glass workers	Diabetes as a cause of death	Odds ratio for diabetes death was 1.4 (0.9–2.1) for glass workers likely exposed to arsenic, comparing with external population.
Rahman et al. (1998)	Cross-sectional, 163 subjects with keratosis indicating arsenic exposure versus 854 unexposed subjects	Bangladesh	Environment: Tube well water	Three steps: symptoms, glucosuria and oral glucose tolerance test	For those with time-weighted mean arsenic exposure levels of <0.5, 0.5–1.0 and >1.0 mg/l, the corresponding prevalence ratios were 2.6 (1.2–5.7), 3.9 (1.8–8.2) and 8.8 (2.7–28.4), while compared with the unexposed subjects
Rahman et al. (1999)	Cross-sectional, 430 exposed subjects with skin lesions versus 114 unexposed subjects	Bangladesh	Environment: Tube well water	Glucosuria	The respective prevalence ratios for those with skin lesions in the categories of arsenic exposure of <1.0, 1.0–5.0, >5.0–10.0 and >10.0 mg years/l were 0.8 (0.3–1.9), 1.7 (0.9–2.9), 2.1 (1.0–4.0), and 2.9 (1.6–5.2)

the subjects were diagnosed by an oral glucose tolerance test without significant clinical symptoms.

The biologic plausibility can be demonstrated by a recent study which showed a higher concentration of glycated hemoglobin (5.4%) in 40 workers exposed to arsenic (taxidermists and persons impregnating or working with arsenic impregnated wood), while compared with a group of 26 controls having glycated hemoglobin of 4.4% (Jensen and Hansen, 1998). This study suggests that arsenic exposure has an influence on glucose metabolism.

In conclusion, the association between arsenic exposure and diabetes mellitus can be observed in different studies carried out in different ethnic groups during different study periods. Different routes of arsenic exposure from drinking water in the Taiwanese and Bangladeshi studies, and from inhalation of polluted air in copper smelters and workers in glass industry in Sweden all resulted in consistent findings of this association. The recent study by Tseng et al. (2000b) demonstrated clearly the correctness of temporality in the assessment of cause-effect. However, there are still some limitations in the reported research works that may reduce the strength of the association. The pathophysiological mechanisms are not known and further investigations are necessary.

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