Prevalence of Non-Insulin-Dependent Diabetes Mellitus and Related Vascular Diseases in Southwestern Arseniasis-Endemic and Nonendemic Areas in Taiwan

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There is evidence indicating that ingestion of arsenic may predispose the development of diabetes mellitus in arsenic-endemic areas in Taiwan. However, the prevalence of diabetes and related vascular diseases in the entire southwestern arseniasis-endemic and nonendemic areas remains to be elucidated. We used the National Health Insurance Database for 1999–2000 to derive the prevalence of non-insulin-dependent diabetes and related vascular diseases by age and sex among residents in southwestern arseniasis-endemic and nonendemic areas in Taiwan. The study included 66,667 residents living in endemic areas and 639,667 in nonendemic areas, all ≥ 25 years of age. The status of diabetes and vascular diseases was ascertained through disease diagnosis and treatment prescription included in the reimbursement claims of clinics and hospitals. The prevalence of non-insulin-dependent diabetes, age- and gender-adjusted to the general population in Taiwan, was 7.5% (95% confidence interval, 7.4–7.7%) in the arseniasis-endemic areas and 3.5% (3.5–3.6%) in the nonendemic areas. Among both diabetics and nondiabetics, higher prevalence of microvascular and macrovascular diseases was observed in arseniasis-endemic than in the nonendemic areas. Age- and gender-adjusted prevalence of microvascular disease in endemic and nonendemic areas was 20.0% and 6.0%, respectively, for diabetics, and 8.6% and 1.0%, respectively, for nondiabetics. The corresponding prevalence of macrovascular disease was 25.3% and 13.7% for diabetics, and 12.3% and 5.5% for nondiabetics. Arsenic has been suggested to increase the risk of non-insulin-dependent diabetes mellitus and its related micro- and macrovascular diseases. *Key words:* arsenic, diabetic complications, environmental health, epidemiology, health insurance, non-insulin-dependent diabetes mellitus, vascular diseases. *Environ Health Perspect* 111:155–159 (2003). [Online 31 October 2002]

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Arsenic is a ubiquitous element in the environment, with metalloid properties. In many parts of the world, arsenic is present in drinking water from wells drilled in ground strata containing the element (IARC 1980; WHO 1981). It is also widely present in the groundwater supply in the United States (Welch et al. 1999).

Long-term exposure to ingested arsenic may induce many health effects. Biologic gradients between ingested arsenic and skin and various internal cancers have been well-documented and used to derive the maximum contamination level of arsenic in drinking water by the U.S. Environmental Protection Agency (Chen et al. 1988a, 1997b; Morales et al. 2000; Tsai et al. 1998). Other chronic health effects induced by arsenic have also drawn global attention, especially cardiovascular, neurologic, reproductive, and developmental hazards (Chen et al. 1997a, 1999). Mortality and morbidity of vascular diseases, including peripheral vascular disease, cerebral infarction, and ischemic heart disease, have been documented to be associated with arsenic levels in drinking water in the arseniasis-endemic area (Chen et al. 1988b, 1996; Chiou et al. 1997b; Tseng et al. 1996; Wang et al. 2002; Wu et al. 1989). The associations between long-term exposure to arsenic and microvascular diseases, including renal disease, retinopathy, and neuropathy, remain to be elucidated. Epidemiologic studies have shown a dose–response relationship between arsenic in drinking water and prevalence and mortality of diabetes mellitus in southwestern Taiwan (Lai et al. 1994; Tsai et al. 1999). Similar findings have been reported in Sweden (Rahman and Axelson 1995; Rahman et al. 1995), Bangladesh (Rahman et al. 1998), and the United States (Lewis 1999). In Taiwan, the incidence of diabetes mellitus was reported to be three to five times higher among residents in the southwestern arseniasis-endemic area compared with those in a nonendemic area (Tseng et al. 2000; Wang et al. 1997). However, no studies have been done to differentiate types of diabetes mellitus associated with arsenic. Diabetes mellitus has been documented to induce stroke, ischemic heart disease, peripheral vascular disease, nephropathy, retinopathy, and neuropathy through both macrovascular and microvascular damage (Chait and Bierman 1994; King and Banskota 1994; Krolewski et al. 1994). It remains to be revealed whether the prevalence of vascular diseases of diabetics is different between arsenic-exposed and unexposed groups. The interactive effects of arsenic and diabetes mellitus on micro- and macrovascular diseases should be closely examined.

Medical records for more than a million individuals in 1999–2000 have been released from the National Health Insurance for academic research in Taiwan. We used this database to estimate prevalence of non-insulin-dependent diabetes mellitus and its related vascular diseases in arseniasis-endemic and nonendemic areas in Taiwan.

Materials and Methods

National Health Insurance Database. In this study we used individual-based reimbursement claims randomly selected from the National Health Insurance Database, which was collected by the Bureau of National Health Insurance and compiled by the National

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This study is based, in part, on data obtained from the National Health Insurance Research Database, which were provided by the Bureau of National Health Insurance, Department of Health, and managed by National Health Research Institutes in Taiwan. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

The scientific contents of this manuscript have been reviewed and approved for publication by the Division of Environmental Health and Occupational Medicine of the National Health Research Institutes. Approval for publication does not necessarily signify that the contents reflect the view and policies of the DEHOM/NHRI, or condemnation or endorsement and recommendation for use on this issue presented.

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Health Research Institutes in Taiwan. The National Health Insurance in Taiwan is compulsory and universal and provides comprehensive health benefits (Chiang 1997). Since 1995, more than 96% of the total population of Taiwan has been covered by the National Health Insurance system [Department of Health (DOH) 1995–1999]. Ninety-three percent of all health providers have been contracted to the Bureau of National Health Insurance, and those not contracted provide much fewer health services [DOH and British Columbia Ministry of Health (BCMH) 1999]. The copayment rate for patients is as low as 8–20%, with a fixed charge of $1.40 U.S. Thus, almost all the people, particularly those affected with chronic diseases, have been using the contracted health providers (Cheng and Chiang 1997). More than 96% of the population, in different age and gender groups, who were covered by National Health Insurance have used health services at least once through contracted health providers during 1999–2000 (DOH 2002). Therefore, the information from the National Health Insurance Database is considered appropriate to derive accurate prevalence rates of chronic diseases such as diabetes mellitus and vascular diseases.

In this study, we used individual-based reimbursement claims from the data file of clinical diagnosis and treatment and the data file of medical prescriptions. The diagnosis of disease status was made from *International Classification of Diseases, Revision 9* (ICD-9) codes recorded in the clinical diagnosis and treatment and from drug names in the medical prescriptions.

In Taiwan, insulin-dependent diabetes mellitus is classified as a severe disease. A severe disease card is issued to people with such diseases, which entitles patients to free medical treatment. We used the data file of patients with severe disease cards to exclude insulin-dependent diabetics from all diabetic patients. The diabetics in this study all had the non-insulin-dependent type.

Southwestern arseniasis-endemic area. The study population in the endemic area included all those who have lived in four southwestern townships: Puttee and Ichu of Chimayo County and Peimen and Hsuehchia of Taiwan County. The water from a large proportion of artesian wells in these four townships had arsenic concentrations > 0.35 mg/L according to a national survey of more than 90% of wells in Taiwan (Chang et al. 1991). This arseniasis-endemic area has been described in detail in a previous report (Chen et al. 1988b). A total of 66,667 residents ≥ 25 years of age in the arseniasis-endemic area were included in this study.

Nonendemic area. Taiwan has 323 rural and urban townships and metropolitan precincts. In this study, the nonendemic area included 313 of them, excluding four townships in the above-defined arseniasis-endemic area and another six neighboring townships: Liuchiao of Chimayo County and Hsinying, Hsiaying, Anting, Chiang-chun, and Yenshui of Taiwan County. Because some artesian wells have arsenic concentrations > 0.35 mg/L and because a few cases of blackfoot disease were identified in these neighboring townships, they were excluded to define the nonendemic area more appropriately. Because the complete files from the original database during 1999–2000 were too large to be managed and analyzed, the National Health Insurance released a sampled database for research use, in which a proportional systematic sampling was used to retrieve one in every 500 records from the two original reimbursement data files. A total of 639,667 residents ≥ 25 years of age in nonendemic area were included in this study.

Disease ascertainment. Diabetics were defined as patients diagnosed with an ICD-9 code of 250 or an ICD-9 A-code (abridged code) of A181. Both microvascular and macrovascular diseases related to diabetes mellitus were also defined by the ICD-9 codes indicated in data files. The microvascular diseases included renal diseases (ICD-9 codes 250.3, 581.8, 582.8, 583.8, 585.0, and 586.0), retinopathy (ICD-9 codes 250.4, 362.0, 362.01, 362.02, and 366.4), and neuropathy (ICD-9 codes 250.5, 357.2, 358.1, and 355). The macrovascular diseases included coronary artery diseases (ICD-9 codes 410 and 411–414), cerebrovascular diseases (ICD-9 codes 430–438), and peripheral vascular diseases (ICD-9 codes 250.6, 785.4, 443.8).

Statistical methods. The prevalence of diabetes mellitus and vascular diseases was first derived for specific age and gender groups by dividing the number of persons with a claim for a given disease by the number of persons with at least one reimbursement claim in 1999–2000. The direct method was used to calculate age-adjusted, gender-adjusted, and age- and gender-adjusted prevalence of the diseases. The general population in midyear 2000 in Taiwan was used as standard population for age and gender adjustment. Prevalence odds ratios and their 95% confidence intervals (CIs) were calculated to indicate the association between arsenic exposure and prevalence of diabetes and vascular diseases.

Results

Prevalence of diabetes mellitus. There was an increasing trend of diabetes mellitus prevalence with age in both arseniasis-endemic and nonendemic areas, as shown in Table 1. The prevalence in the arseniasis-endemic area was consistently greater than in the nonendemic area across all five age groups for both men and women. The prevalence odds ratios of diabetes in the endemic area in comparison with the nonendemic area were consistently greater in women than in men for all age groups, as shown in Figure 1. After adjustment for age and sex, the prevalence odds ratio was 2.69 (95% CI, 2.65–2.73) in the arseniasis-endemic area, using the nonendemic area as the referent.

Prevalence of vascular diseases in diabetics and nondiabetics. An increasing trend with age for microvascular disease prevalence was observed among diabetics and nondiabetics in both arseniasis-endemic and nonendemic areas for both men and women, as

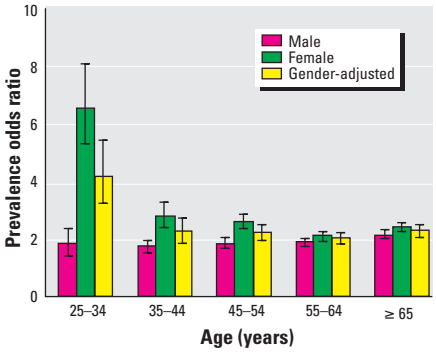

Figure 1. Prevalence odds ratios for diabetes mellitus in arseniasis-endemic versus nonendemic areas, by age and sex. Error bars indicate 95% CI.

Table 1. Prevalence of diabetes mellitus (%) by age and sex in southwestern arseniasis-endemic and nonendemic areas in Taiwan.

	Arseniasis-endemic area			Nonendemic areas		
	Male	Female	Gender-adjusted	Male	Female	Gender-adjusted
Age (years)	Prevalence (*n*)	Prevalence (*n*)	prevalence (95% CI)	Prevalence (*n*)	Prevalence (*n*)	prevalence (95% CI)
25–34	1.08 (7,892)	1.89 (7,362)	1.48 (1.29–1.67)	0.60 (40,535)	0.29 (78,438)	0.45 (0.41–0.49)
35–44	3.77 (8,148)	2.89 (7,170)	3.34 (3.06–3.64)	2.22 (54,509)	1.04 (79,860)	1.64 (1.57–1.71)
45–54	10.04 (5,667)	9.25 (5,776)	9.65 (9.11–10.19)	5.59 (47,129)	3.63 (70,557)	4.62 (4.50–7.88)
55–64	14.43 (5,781)	15.77 (6,543)	15.1 (14.48–15.74)	7.82 (43,451)	7.63 (59,373)	7.72 (7.56–7.89)
≥ 65	15.38 (5,644)	21.18 (6,684)	18.13 (17.45–18.81)	7.28 (85,442)	8.90 (80,353)	8.05 (7.92–8.18)
Age-adjusted prevalence (95% CI)	7.18 (6.92–7.44)	7.92 (7.66–8.18)	7.54 (7.35–7.73)	3.82 (3.75–3.89)	3.21 (3.16–3.26)	3.52 (3.48–3.56)

shown in Table 2. For all five age groups in both men and women, the prevalence of microvascular diseases was consistently highest among diabetics in the arseniasis-endemic area, followed by nondiabetics in the endemic area, diabetics in the nonendemic area, and nondiabetics in the nonendemic area. Similar findings were observed for macrovascular diseases (Table 3): diabetics in the arseniasis-endemic area had the highest prevalence, followed by diabetics in nonendemic area, nondiabetics in endemic area, and nondiabetics in nonendemic area for most age groups in men and women. Figure 2 shows the prevalence odds ratios of microvascular diseases among diabetics of the endemic area (using the 55–64 age range as a typical example, the odds ratio is 15.6; 95% CI, 13.4–18.0), nondiabetics of the endemic area (7.0; 95% CI, 6.3–7.9), and diabetics of the nonendemic area (5.1; 95% CI, 4.4–5.9) in comparison with nondiabetics of the nonendemic area. The odds ratios tended to be higher in women than in men before 65 years of age but without statistical significance. Figure 3 illustrates the prevalence odds ratios of macrovascular diseases in the four diabetes-area groups by age and sex. The prevalence odds ratios increased from nondiabetics in the nonendemic area (for ages 55–64), to nondiabetics in the endemic area (2.0; 95% CI, 1.9–2.2), to diabetics in the nonendemic area (1.7; 95% CI, 1.6–1.8), to diabetics in the endemic area (3.7; 95% CI, 3.3–4.0) for most age groups in men and women. The odds ratios tended to be higher in women than in men before 65 years of age, with statistical significance.

The prevalence of various vascular diseases among diabetics and nondiabetics in endemic and nonendemic areas is shown in Table 4. The prevalence of all vascular diseases studied was much higher among diabetics than among nondiabetics and significantly higher in the arseniasis-endemic area than in the nonendemic area. The prevalence odds ratios of these vascular diseases in the arseniasis-endemic area compared with the nonendemic area ranged from 1.22 (95% CI, 1.10–1.35) for peripheral vascular disease to 7.21 (95% CI, 6.51–7.97) for neurologic disorder among diabetics, and from 1.34 (95% CI, 1.29–1.39) for coronary heart disease to 13.97 (95% CI, 13.38–14.58) for neurologic disorder among diabetics.

Table 2. Prevalence of microvascular diseases (%) by age and sex among diabetics and nondiabetics in the southwestern arseniasis-endemic and nonendemic areas in Taiwan.

	Arseniasis-endemic area		Nonendemic area	
Sex, age (years)	Diabetics Prevalence (*n*)	Nondiabetics Prevalence (*n*)	Diabetics Prevalence (*n*)	Nondiabetics Prevalence (*n*)
Male				
25–34	9.41 (85)	4.98 (7,807)	3.72 (242)	0.79 (40,293)
35–44	18.89 (307)	7.21 (7,841)	5.95 (1,210)	0.99 (53,299)
45–54	20.56 (569)	9.06 (5,098)	6.11 (2,633)	1.23 (44,496)
55–64	23.14 (834)	10.47 (4,947)	7.56 (3,398)	1.49 (40,053)
≥ 65	25.23 (868)	10.01 (4,776)	7.45 (6,218)	1.52 (79,224)
Age-adjusted prevalence (95% CI)	18.08 (15.86–20.30)	7.75 (7.45–8.05)	5.78 (5.71–6.55)	1.12 (1.08–1.16)
Female				
25–34	14.39 (139)	6.49 (7,223)	5.75 (226)	0.47 (78,212)
35–44	24.15 (207)	9.36 (6,963)	5.52 (833)	0.78 (79,027)
45–54	23.41 (534)	10.91 (5,242)	7.03 (2,562)	1.10 (67,995)
55–64	27.13 (1,032)	11.74 (5,511)	7.35 (4,523)	1.46 (54,841)
≥ 65	25.00 (1,416)	11.03 (5,268)	7.07 (7,155)	1.64 (73,198)
Age-adjusted prevalence (95% CI)	21.87 (19.47–24.27)	9.42 (9.09–9.75)	6.31 (5.36–7.26)	0.96 (0.93–0.99)
Age and gender-adjusted prevalence (95% CI)	19.95 (18.31–21.58)	8.57 (8.35–8.80)	6.04 (5.44–6.65)	1.04 (1.01–1.07)

Table 3. Prevalence of macrovascular diseases (%) by age and gender among diabetics and nondiabetics in southwestern arseniasis-endemic and nonendemic areas in Taiwan.

	Arseniasis-endemic area		Nonendemic area	
Sex, age (years)	Diabetics Prevalence (*n*)	Nondiabetics Prevalence (*n*)	Diabetics Prevalence (*n*)	Nondiabetics Prevalence (*n*)
Male				
25–34	12.94 (85)	5.15 (7,807)	7.85 (242)	2.35 (40,293)
35–44	14.33 (307)	6.50 (7,841)	10.33 (1,210)	3.80 (53,299)
45–54	26.89 (569)	10.47 (5,098)	15.46 (2,633)	6.71 (44,496)
55–64	36.09 (834)	16.76 (4,947)	19.98 (3,398)	9.83 (40,053)
≥ 65	45.51 (868)	28.75 (4,776)	25.84 (6,218)	13.46 (79,224)
Age-adjusted prevalence (95% CI)	23.42 (21.03–25.81)	11.31 (10.97–11.65)	14.02 (12.94–15.10)	6.07 (5.98–6.16)
Female				
25–34	21.58 (139)	9.80 (7,223)	7.08 (226)	1.64 (78,212)
35–44	16.91 (207)	7.42 (6,963)	10.08 (833)	2.62 (79,027)
45–54	28.09 (534)	10.97 (5,242)	14.75 (2,562)	4.68 (67,995)
55–64	38.28 (1,032)	19.00 (5,511)	19.66 (4,532)	8.02 (54,841)
≥ 65	47.74 (1,416)	30.30 (5,268)	25.13 (7,155)	12.91 (73,198)
Age-adjusted prevalence (95% CI)	27.13 (24.65–29.61)	13.25 (12.88–13.62)	13.40 (12.29–14.51)	4.81 (4.74–4.88)
Age and gender-adjusted prevalence (95% CI)	25.25 (23.53–26.97)	12.26 (12.01–12.51)	13.72 (12.95–14.49)	5.45 (5.39–5.51)

Discussion

This study confirmed the findings of our previous study (Lai et al. 1994) in which the subjects in the arseniasis-endemic area had an elevated prevalence of diabetes compared with the nonendemic area (odds ratio = 2.7 after adjustment for age and sex). In this study we found that women tended to have a higher prevalence of diabetes than did men in the arseniasis-endemic area but not in the nonendemic area. Furthermore, in the arseniasis-endemic area, women had a statistically significantly higher age-adjusted prevalence of vascular diseases than did men (9.4% vs. 7.8% for microvascular disease and 13.3% vs. 11.3% for macrovascular disease) among the nondiabetics. Also, women have been found to drink less water than men. The hypothesis of a greater vulnerability to arsenic exposure in women than in men needs further investigation.

In a national diabetes survey (Pan et al. 1998) applying both fasting glucose and oral glucose tolerance tests, the diabetes prevalence for men ≥ 65 years of age in Taiwan was 7.6%. The diabetes prevalence for the same age group of men in this study was 8.1%, which is similar to that observed by Pan et al. (1998). The diabetes prevalence was also compatible with that observed in the United States [National Health and Nutrition Examination Survey (NHANES)] (Harris et al. 1987) and in Japan (Kuzuya 1994). Diabetes prevalence by age and sex in the southwestern arseniasis-endemic area in this study is also similar to that observed in a previous survey conducted in the same endemic area (Lai et al. 1994).

Arsenic has been proposed to induce insulin-dependent and non-insulin-dependent diabetes, probably through increased oxidative stress (Longnecker and Daniels 2001; Wu et al. 2001). Oxidative stress has been found to induce the development of insulin resistance and endothelial dysfunction by the observations of normal, impaired glucose-tolerant, and diabetic subjects (Gopaul et al. 2001). Hypertension, an important component of insulin resistance syndrome, has also been found to be associated with long-term ingested arsenic exposure (Chen et al. 1995). It is essential to evaluate insulin secretion and insulin sensitivity in subjects with various degrees of arsenic exposure, taking genetic susceptibility (Chiou et al. 1997a) into account.

Phenylarsine oxide binding to sulfhydryl groups (–SH) has been found to induce insulin resistance (Frost and Lane 1985; (Henriksen and Holloszy 1990) via the increase of cell stress and reduction of glucose

transport proteins, especially for GLUT4 and GLUT1, and glucose uptake (Jhun et al. 1991). However, phenylarsine oxide is an artificial organic form of arsenic used mainly for testing the role of the sulfhydryl group in insulin resistance. The use of natural arsenic compounds such as arsenite, arsenate, and/or methylated forms for such studies has been suggested. There are no consistent changes in glucose levels in experimental studies. Plasma glucose and triglycerides were the lowest in mice with high arsenate exposure administered via drinking water (Hughes and Thompson 1996). Enhanced glucose uptake was found in response to arsenite (100 μM for up to 180 min) in bovine chromaffin cells (Fladeby and Serck-Hanssen 1999). Nonetheless, intraperitoneal administration of sodium arsenite of 1.0 mg/kg has been found to cause significantly higher blood glucose in guinea pigs at 1 and 2 hr (Mitchell et al. 2000). Organic arsenic was found to induce the inhibition of glucose uptake (Liebl et al. 1995). Studies using long-term treatment of well-specified arsenic species are necessary for future conclusions. Arsenic-induced oxidative stress, mainly through the depletion of glutathione (Suzuki et al. 2001), has been proposed to cause both insulin resistance and atherosclerosis (del Razo et al. 2001), and the latter may be profound in hyperglycemia or diabetic states (Curcio and Ceriello 1992; Lorenzi 1992).

The finding of a strikingly increased prevalence of macrovascular diseases observed in the arseniasis-endemic area compared with the nonendemic area is consistent with our previous findings of arsenic-induced atherosclerosis (Chen et al. 1988b, 1996; Chiou et al. 1997b; Tseng et al. 1996; Wang et al. 2002; Wu et al. 1989). There have been few studies comparing the prevalence of specific vascular diseases in relation to arsenic exposure in diabetics and nondiabetics. Age-adjusted prevalence of cerebrovascular disease in the Lanyang Basin, a recently identified northeastern endemic area of arseniasis in Taiwan, was 15.8% for men and 13.2% for women (Chiou et al. 1997b). The two figures were between those found in the present study: 21.4% for diabetics and 8.7% for nondiabetics. Diabetes was associated with an increased risk of cerebrovascular disease showing an age- and gender-adjusted odds ratio of 1.8 in the northeastern endemic area and 2.4 (21.35 ÷ 8.72) in the southwestern endemic area of this study. A previous study showed a dose–response relationship between ingested arsenic and peripheral vascular diseases (Wang et al. 2002). The present study demonstrated the odds ratios of 1.2 (95% CI, 1.1–1.4) in diabetics and 12.5 (95% CI, 9.5–16.5) in nondiabetics. Arsenic, mainly trivalent arsenicals (e.g., arsenite), may induce atherosclerosis through damage of endothelial cells or smooth muscle cells by intracellular-reduced glutathione or through oxidative DNA damage (Chang et al. 1991; Chiou et al. 1997a; Lynn et al. 2000; Wu et al. 2001). Further studies are necessary to test the hypothesis that arsenic induces renal (Mitchell et al. 2000) and neural (Brouwer et al. 1992; Mahajan et al. 1992) damage directly or through angiopathy.

The National Health Insurance Database used in this study consisted of reimbursement claims of all patients who had received care from contracted clinics and/or hospitals at least once in 1999–2000. Therefore, those who were not cared for by contracted hospitals or clinics during the study period were excluded

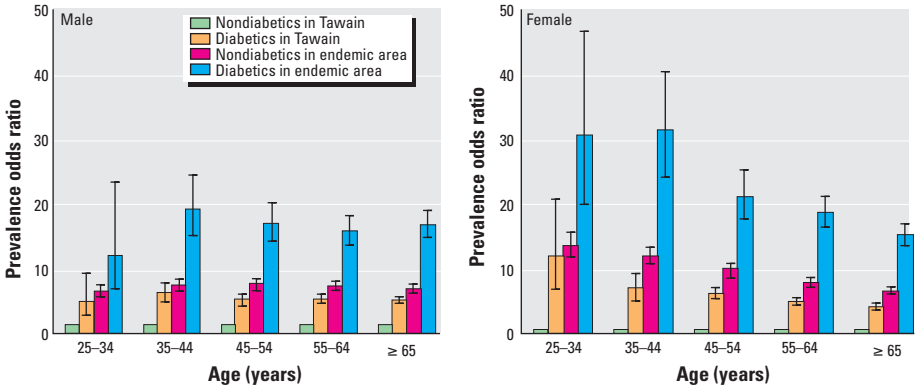

Figure 2. Prevalence odds ratios for microvascular diseases among diabetics and nondiabetics in the endemic area and diabetics in the nonendemic area, compared with nondiabetics in the nonendemic area, by age and sex. Error bars indicate 95% CI.

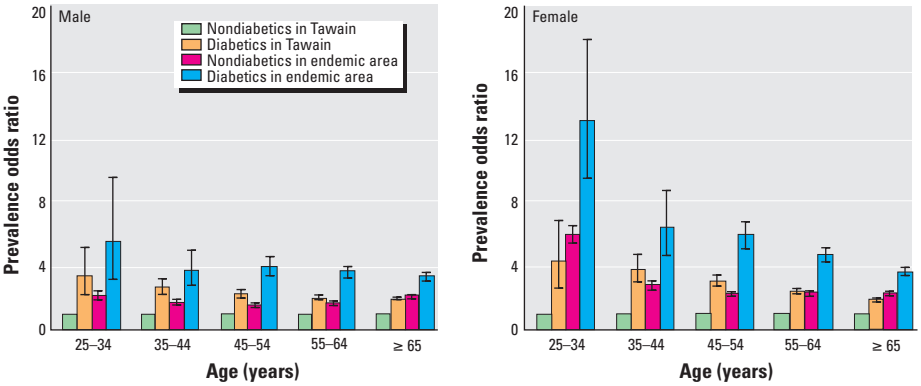

Figure 3. Prevalence odds ratios for macrovascular diseases among diabetics and nondiabetics in the endemic area and diabetics in the nonendemic area, compared with nondiabetics in the nonendemic area, by age and sex. Error bars indicate 95% CI.

Table 4. Age and gender-adjusted prevalence of various vascular complications among diabetics and nondiabetics in arseniasis-endemic and nonendemic areas in Taiwan.

Disease	Age and gender-adjusted prevalence (%) Arseniasis-endemic area	Arseniasis-nonendemic area	Prevalence odds ratio in endemic area compared with nonendemic area (95% CI)	*p*-Value
Diabetics				
Renal disease[a]	3.19	1.17	2.78 (2.32–3.33)	< 0.001
Retinopathy[b]	7.88	3.86	2.13 (1.91–2.38)	< 0.001
Neurologic disorders[c]	15.61	2.50	7.21 (6.51–7.97)	< 0.001
Peripheral vascular disease[d]	8.33	6.92	1.22 (1.10–1.35)	< 0.001
Cerebrovascular disease[e]	21.35	7.77	3.22 (2.99–3.47)	< 0.001
Coronary artery disease[f]	16.16	7.43	2.40 (2.21–2.61)	< 0.001
Nondiabetics				
Renal disease[a]	0.61	0.41	1.49 (1.33–1.66)	< 0.001
Retinopathy[b]	—	—[g]	—	—
Neurologic disorder[c]	8.22	0.64	13.97 (13.38–14.58)	< 0.001
Peripheral vascular disease[d]	0.18	0.01	12.50 (9.47–16.48)	< 0.001
Cerebrovascular disease[e]	8.72	2.49	3.74 (3.62–3.87)	< 0.001
Coronary artery disease[f]	5.68	4.31	1.34 (1.29–1.39)	< 0.001

[a]ICD-9 codes 250.3, 581.8, 582.8, 583.8, 585.0, and 586.0. [b]ICD-9 codes 250.4, 362.0, 362.1, 362.2, and 366.4. [c]ICD-9 codes 250.5, 357.2, 358.1, and 355. [d]ICD-9 codes 250.6, 785.4, and 443.8. [e]ICD-9 codes 430–438. [f]ICD-9 codes 410 and 411–414. [g]Sample size of the disease cases was too small for valid statistical analysis.

from the database. However, more than 96% of insured people had ever received care from contracted hospitals and clinics. The prevalence estimated in this study was considered reasonably correct. The disease prevalence might be overestimated if patients are more likely to visit clinicians and to be included in the database than are unaffected people. Nonetheless, the odds ratio comparing arseniasis-endemic and nonendemic areas would be valid if the frequencies of visiting clinicians were the same between two comparison areas.

Considering the rural and urban differences in lifestyles and disease patterns, residents in the rural area were considered less likely to develop cardiovascular diseases as a result of decreased prevalence of risk factors from dietary intake, obesity, and physical activity (Singh et al. 1998). However, residents in the arseniasis-endemic area had a higher prevalence of cardiovascular disease despite the fact that the endemic area was more rural than was the nonendemic area in Taiwan. Thus, the vascular effect of ingested arsenic observed in this study was based on a conservative comparison.

Conclusions

This study demonstrated that residents in the arseniasis-endemic area had an increased risk of diabetes and its related vascular diseases compared with those in the nonendemic area. This study also found a larger contribution of ingested arsenic than of diabetes on the development of microvascular diseases. Future studies will be directed to mechanistic investigations of arsenic inducing non-insulin-dependent diabetes and atherosclerosis. Risk assessment of arsenic exposure for diabetes and the related vascular diseases should be integrated with the current scheme for cancer risk from arsenic.

References

Brouwer OF, Onkenhout W, Edelbroek PM, de Kom JF, de Wolff FA, Peters AC. 1992. Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. Clin Neurol Neurosurg 94:307–310.

Chait A, Bierman EL. 1994. Pathogenesis of macrovascular disease in diabetes. In: Joslin's Diabetes Mellitus (Kahn CR, Weir GC, eds). 13th ed. Philadelphia:Lea & Febiger, 648–664.

Chang WC, Chen SH, Wu HL, Shi GY, Murota S, Morita I. 1991. Cytoprotective effect of reduced glutathione in arsenical-induced endothelial cell injury. Toxicology 69:101–110.

Chen CJ, Chiou HY, Chiang MH, Lin LJ, Tai TY. 1996. Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. Arterioscler Thromb Vasc Biol 16:504–510.

Chen CJ, Chiou HY, Huang WI, Chen SY, Hsueh YM, Tseng CH, et al. 1997a. Systemic non-carcinogenic effects and developmental toxicity of inorganic arsenic. In: Arsenic: Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). London:Chapman & Hall, 124–134.

Chen CJ, Hsu LI, Tseng CH, Hsueh YM, Chiou HY. 1999. Emerging epidemics of arseniasis in Asia. In: Arsenic Exposure and Health Effects (Chappell WR, Abemathy CO, Calderon RL, eds). New York:Elsevier Science, 113–121.

Chen CJ, Hsueh YM, Chiou HY, Hsu YH, Chen SY, Horng SF, et al. 1997b. Human carcinogenicity of inorganic arsenic. In: Arsenic: Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). London: Chapman & Hall, 232–242.

Chen CJ, Hsueh YM, Lai MS, Shyu MP, Chen SY, Wu MM, et al. 1995. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25:53–60.

Chen CJ, Kuo TL, Wu MM. 1988a. Arsenic and cancers. Lancet 1(8582):414–415.

Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, Wu HY. 1988b. Atherogenicity and carcinogenicity of high-arsenic artesian well water—multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 8:452–460.

Cheng SH, Chiang TL. 1997. The effect of universal health insurance on health care utilization in Taiwan. Results from a natural experiment. JAMA 278:89–93.

Chiang TL. 1997. Taiwan's 1995 health care reform. Health Policy 39:225–239.

Chiou HY, Hsueh YM, Hsieh LL, Hsu LL, Hsu YH, Hsieh FI, et al. 1997a. Arsenic methylation capacity, body retention, and null genotypes of glutathione *S*-transferase M1 and T1 among current arsenic-exposed residents in Taiwan. Mutat Res 386:197–207.

Chiou HY, Huang WI, Su CL, Chang SF, Hsu YH, Chen CJ. 1997b. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 28:1717–1723.

Curcio F, Ceriello A. 1992. Decreased cultured endothelial cell proliferation in high glucose medium is reversed by antioxidants: new insights on the pathophysiological mechanisms of diabetic vascular complications. In Vitro Cell Dev Biol 28A:787–790.

del Razo LM, Quintanilla-Vega B, Brambila-Colombres E, Calderon-Aranda ES, Manno M, Albores A. 2001. Stress proteins induced by arsenic. Toxicol Appl Pharmacol 177:132–148.

DOH. 1995–1999. National Health Insurance Annual Statistical Report. Taipei, Taiwan:Bureau of National Health Insurance, Department of Health.

———. 2002. About the Program. Taipei, Taiwan:Bureau of National Health Insurance, Department of Health. Available: http://www.nhi.gov.tw/00english/e_index.htm [accessed 20 June 2002].

DOH and BCMH. 1999. First Report on National Health Insurance Health Care Service Analyses for the International Collaborative Project of Business, Technical and Informatics Consulting Services. Taipei, Taiwan:Bureau of National Health Insurance, Department of Health/Victoria, BC:British Columbia Ministry of Health.

Fladeby C, Serck-Hanssen G. 1999. Stress-induced glucose uptake in bovine chromaffin cells: a comparison of the effect of arsenite and anisomycin. Biochim Biophys Acta 1452:313–321.

Frost SC, Lane MD. 1985. Evidence for the involvement of vicinal sulfhydryl groups in insulin-activated hexose transport by 3T3-L1 adipocytes. J Biol Chem 260:2646–2652.

Gopaul NK, Manraj MD, Hebe A, Lee Kwai Yan S, Johnston A, et al. 2001. Oxidative stress could precede endothelial dysfunction and insulin resistance in Indian Mauritians with impaired glucose metabolism. Diabetologia 44:706–712.

Harris AI, Hadden WC, Knowler WC, Bennett PH. 1987. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20–74 years. Diabetes Care 36:523–534.

Henriksen EJ, Holloszy JO. 1990. Effects of phenylarsine oxide on stimulation of glucose transport in rat skeletal muscle. Am J Physiol 258(4 pt 1):C648–C653.

Hughes MF, Thompson DJ. 1996. Subchronic dispositional and toxicological effects of arsenate administered in drinking water to mice. J Toxicol Environ Health 49:177–196.

IARC. 1980. Some Metals and Metallic Compounds. IARC Monogr Eval Carcinog Risks Hum 23:39–141.

Jhun BH, Hah JS, Jung CY. 1991. Phenylarsine oxide causes an insulin-dependent, GLUT4-specific degradation in rat adipocytes. J Biol Chem 266:22260–22265.

King GL, Banskota NK. 1994. Mechanisms of diabetic microvascular complications. In: Joslin's Diabetes Mellitus (Kahn CR, Weir GC, eds). 13th ed. Philadelphia:Lea & Febiger, 631–647.

Krolewski AS, Warram JH. 1994. Onset of the complications of diabetes—epidemiology of late complications of diabetes. In: Joslin's Diabetes Mellitus (Kahn CR, Weir GC, eds). 13th ed. Philadelphia:Lea & Febiger, 605–619.

Kuzuya T. 1994. Prevalence of diabetes mellitus in Japan compiled from literature. Diabetes Res Clin Pract 24:S15–S21.

Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, et al. 1994. Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 139:484–492.

Lewis DR. 1999. Drinking water arsenic: the Millard County, Utah mortality study. In: Arsenic Exposure and Health Effects (Chappell WR, Abernathy CO, Calderon RL, eds). New York:Elsevier, 133–140.

Liebl B, Muckter H, Doklea E, Fichtl B, Forth W. 1995. Influence of 2,3-dimercaptopropanol and other sulfur compounds on oxophenylarsine-mediated inhibition of glucose uptake in MDCK cells. Analyst 120:771–774.

Longnecker MP, Daniels JL. 2001. Environmental contaminants as etiologic factors for diabetes. Environ Health Perspect 109(suppl 6):871–876.

Lorenzi M. 1992. Glucose toxicity in the vascular complications of diabetes: the cellular perspective. Diabetes Metab Rev 8:85–103.

Lynn S, Gurr JR, Lai HT, Jan KY. 2000. NADH oxidase activation is involved in arsenite-induced oxidative DNA damage in human vascular smooth muscle cells. Circ Res 86:514–519.

Mahajan SK, Aggarwal HK, Wig N, Maitra S, Chugh SN. 1992. Arsenic induced neuropathy. J Assoc Physicians India 40:268–269.

Mitchell RD, Ayala-Fierro F, Carter DE. 2000. Systemic indicators of inorganic arsenic toxicity in four animal species. J Toxicol Environ Health A 59:119–134.

Morales KH, Ryan L, Kuo TL, Wu MM, Chen CJ. 2000. Risk of internal cancers from arsenic in drinking water. Environ Health Perspect 108:655–661.

Pan WH, Yeh WT, Hwu CM, Ho NT. 1998. Diabetes prevalence and recognition in Taiwan. In: National Nutrition Survey 1993–1996 in Taiwan (Pan WH, ed). Taipei, Taiwan:Department of Health, Executive Yuan, 279–290.

Rahman M, Axelson O. 1995. Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. Occup Environ Med 52:773–774.

Rahman M, Tondel M, Ahmad SA, Axelson O. 1998. Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 148:198–203.

Rahman M, Wingren G, Axelson O. 1995. Diabetes mellitus among Swedish art glass workers—an effect of arsenic exposure. Scand J Work Environ Health 22:146–149.

Singh RB, Bajaj S, Niaz MA, Rastogi SS, Moshiri M. 1998. Prevalence of type 2 diabetes mellitus and risk of hypertension and coronary artery disease in rural and urban population with low rates of obesity. Int J Cardiol 66:65–72.

Suzuki KT, Tomita T, Ogra Y, Ohmichi M. 2001. Glutathione-conjugated arsenics in the potential hepato-enteric circulation in rats. Chem Res Toxicol 14:1604–1611.

Tsai SM, Wang TN, Ko YC. 1998. Cancer mortality trends in a blackfoot disease endemic community of Taiwan following water source replacement. J Toxicol Environ Health A 55:389–404.

———. 1999. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch Environ Health 54:186–193.

Tseng CH, Chong CK, Chen CJ, Tai TY. 1996. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. Atherosclerosis 120:125–133.

Tseng CH, Tai TY, Chong CK, Tseng CP, Lai MS, Lin BJ, et al. 2000. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arsenic-hyperendemic villages in Taiwan. Environ Health Perspect 108:847–851.

Wang CH, Jeng JS, Yip PK, Chen CL, Hsu LI, Hsueh YM, et al. 2002. Biological gradient between long-term arsenic exposure and carotid atherosclerosis. Circulation 105:1804–1809.

Wang SL, Pan WH, Hwu CM, Ho LT, Lo CH, Lin SL, et al. 1997. Incidence of NIDDM and the effects of gender, obesity and hyperinsulinaemia in Taiwan. Diabetologia 40:1431–1438.

Welch AH, Helsel DR, Focazio MJ, Watkins SA. 1999. Arsenic in ground water supplies of the United States. In: Arsenic Exposure and Health Effects (Chappell WR, Abernathy CO, Calderon RL, eds). New York:Elsevier, 9–17.

WHO. 1981. Arsenic. Environmental Health Criteria 18. Geneva:World Health Organization.

Wu MM, Chiou HY, Wang TW, Hsueh YM, Wang IH, Chen CJ, et al. 2001. Association of blood arsenic levels with increased reactive oxidants and decreased antioxidant capacity in a human population of northeastern Taiwan. Environ Health Perspect 109:1011–1017.

Wu MM, Kuo TL, Hwang YH, Chen CJ. 1989. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol 130:1123–1132.