

Does Arsenic Exposure Increase the Risk for Diabetes Mellitus?

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Objective: Long-term arsenic exposure has been reported to be associated with prevalence, incidence, and mortality of diabetes mellitus (DM). A tap water supply system was implemented in the early 1960s in the blackfoot disease (BFD) endemic areas. The objective of this study is to examine whether DM mortality decreased after the improvement of drinking water supply system through elimination of arsenic exposure from artesian well water. **Methods:** Standardized mortality ratios (SMRs) for DM were calculated for the BFD endemic area for the years 1971–2000. **Results:** The study results show that mortality from DM declined in females (but not in males) gradually after the improvement of drinking water supply system. **Conclusions:** Based on the reversibility criterion, the association between arsenic exposure and DM is likely to be casual for females but not in males. (J Occup Environ Med. 2006; 48:63–67)

An area along the southwestern coast of Taiwan is known for the endemic occurrence of a peripheral vascular disease. This disease also is known as blackfoot disease (BFD). Clinically, the disease starts with numbness or coldness of one or more extremities and intermittent claudication and ends with gangrene and spontaneous amputation.¹ Although the etiology of BFD remains unclear, BFD has been associated with the consumption of drinking water derived from artesian wells in the endemic areas.² A physicochemical study of artesian well water in the affected area found it contained high levels of arsenic.³ Thus, arsenic has been suggested as the most important risk factor for BFD.⁴

A dose–response relationship between arsenic in drinking water and prevalence and mortality of diabetes mellitus (DM) has been reported in the BFD endemic area.^{5–7} Similar findings have been reported in copper smelter workers⁸ as well as in the art glass industry.⁹ In a community-based survey of DM in Bangladesh, Rahman et al.¹⁰ observed a dose–response trend between the prevalence of DM and the arsenic level in drinking water. The incidence of DM was reported to be three to five times higher among the residents in the BFD endemic areas than those in a nonendemic area.^{11,12}

A tap water supply system was implemented in the early 1960s in the BFD endemic areas, and all of the areas were almost completely supplied with municipal water between 1966 and 1975.¹ Artesian well water was no longer used for drink-

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ing and cooking after mid-1970s. This change provided us with a unique opportunity to examine whether the mortality rates from DM among residents living in the BFD endemic areas would decrease with the intervention of the withdrawal of arsenic exposure.

Materials and Methods

Study Areas

The study area included 4 townships, Peimen, Heuechia, Putai, and Ichu, located on the southwest coast of Taiwan, where BFD has been endemic. The study area and population have been described in a previous report.⁴ Briefly, residents in the study areas consumed high-arsenic artesian well water since 1910. The midyear population in the BFD-endemic area decreased from 139,051 in 1971 to 100,771 in 2000. The arsenic concentration of artesian well water measured in the early 1960s ranged from 0.35 to 1.14 ppm with a median of 0.78 ppm.³ Most residents in the study area were engaged in farming, fishery, and salt production. They share similar socioeconomic status, living environments, lifestyles, dietary patterns, and health service facilities. A tap water supply system was implemented in the early 1960s, but its coverage remained low until the early 1970s. Artesian well water was no longer used for drinking and cooking after the mid-1970s. The current tap water supply for the study area came from the Tzeng-Wen reservoir where the arsenic concentration of water was less than 0.01 ppm.¹³ The standard limit for arsenic in drinking water set by the U.S. Environmental Protection Agency is 0.01 ppm.¹⁴

Data Source and Mortality Analysis

Because it is obligatory to register any birth, death, marriage and divorce, and migration in the household registration office, the population statistics in Taiwan are

highly accurate and complete. Information concerning both the number of kidney cancer deaths and the mid-year population by sex, age, calendar year during the years 1971–2000 was obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health, which is in charge of the death registration system in Taiwan. In this report, diabetes mellitus is defined according to the International Classification of Disease, Injury, and Causes of Death, 9th revision (ICD-9 code 250). Indirect standardization was applied to produce standardized mortality ratios (SMRs) for DM, which is the ratio of the number of DM deaths occurring in the study area to the number expected given the standard rates in each sex and age group. The expected number of deaths is calculated by applying a standard set of age-sex-specific rates to the number of person in each age-sex-specific class in the study area. Age- and sex-specific mortality rates of DM in Taiwan were used as the standard rates to calculate the SMRs.

Statistics

To minimize the statistical instability resulting from sudden changes in DM mortality over time, 3-year moving averages of the SMRs between 1971 and 2000 were calculated. The 3-year sliding means of the SMRs were then plotted on a graph over time.

Results

There were 816 DM deaths in BFD-endemic area between 1971 and 2000; 297 men and 519 women (Table 1). The means of the 3-year SMRs for DM in the study area were appreciably higher than for Taiwan as a whole in both genders. Figure 1 shows the time series plot of the SMRs for men over the course of time. A linear time trend analysis was performed, and the estimated slope for male SMRs (rate of decrease per year) is -0.06 ($P = 0.95$). No significant association with the slope of time trend was detected.

Figure 2 shows the time series plot of the SMRs for women over the course of time. We can see the whole trend of decreasing mortality rates. The SMRs had an average decrease of 1.53 per year from 1971 to 2000 ($P < 0.01$).

Discussion

Because inorganic arsenic has been reported to be associated with an increased mortality from DM, it is logical to expect that a reduction of arsenic exposure through improvement in the water supply system would lead to a decrease in mortality rates from DM in both males and females living in the BFD endemic areas. Our results, however, indicate that the reduction was restricted to women. This finding enabled us to use the reversibility criterion to assess the causal nature for the association between inorganic arsenic and DM.¹⁵ On the basis of this criterion, this finding strengthened the likelihood of an association between arsenic exposure and female DM being causally related.

In the BFD endemic areas, the main exposure to inorganic arsenic is through ingestion of high-arsenic artesian well water. Physical and chemical characteristics of drinking water have been intensively studied in both BFD-endemic and nonendemic areas.³ In artesian well water, the only chemical component exceeding the maximum allowable limits was arsenic. Arsenic is thus the main water-borne chemical responsible for the increased mortality from DM in the endemic area.⁴ Therefore, the reduction in female DM mortality in study area may result from the withdrawal of the arsenic exposure through improvements in the water supply system as reflected by a change in water source.

Mortality data have been widely used to generate epidemiologic hypotheses, despite their inherent limitations.¹⁶ The completeness and accuracy of the death registration system should be evaluated before any conclusion based on the mor-

TABLE 1
SMR for DM in BFD-Endemic Area in Taiwan, 1970–2000

Year	Male				Female			
	No. Deaths Observed	No. Deaths Expected	SMR	Moving Average of 3 Yearly SMRs	No. Deaths Observed	No. Deaths Expected	SMR	Moving Average of 3 Yearly SMRs
1971	3	1.72	174	136	3	3.16	95	92
1972	3	2.02	149	121	5	3.83	131	98
1973	2	2.34	85	71	2	4.01	50	71
1974	3	2.32	129	56	5	4.41	113	112
1975	0	2.13	0	25	2	3.91	51	163
1976	1	2.48	40	67	8	4.63	173	196
1977	1	2.97	34	91	15	5.68	264	176
1978	4	3.15	127	168	9	5.94	152	128
1979	4	3.55	113	155	7	6.18	113	135
1980	11	4.19	263	186	8	6.78	118	146
1981	4	4.51	89	114	14	7.98	175	165
1982	11	5.35	206	124	14	9.71	144	166
1983	3	6.28	48	85	20	11.42	175	156
1984	9	7.61	118	112	22	12.28	179	146
1985	7	7.91	89	121	15	13.32	113	120
1986	10	7.67	130	146	20	13.67	146	121
1987	12	8.41	143	144	15	14.87	101	116
1988	16	9.78	164	146	20	17.29	116	106
1989	12	9.70	124	140	23	17.48	132	104
1990	16	10.61	151	114	12	17.28	69	96
1991	16	11.07	145	106	21	18.68	112	117
1992	6	12.66	47	89	23	21.50	107	118
1993	18	14.26	126	113	30	22.69	132	115
1994	15	15.72	95	115	30	26.27	114	112
1995	23	19.50	118	115	29	29.58	98	107
1996	27	20.59	131	95	38	30.47	125	86
1997	20	20.74	96	74	29	29.60	98	80
1998	12	20.97	57	57	10	28.81	35	77
1999	16	23.70	68	—	38	35.62	107	—
2000	12	25.29	47	—	32	36.11	89	—
Total	297	289.20	103		519	463.16	112	

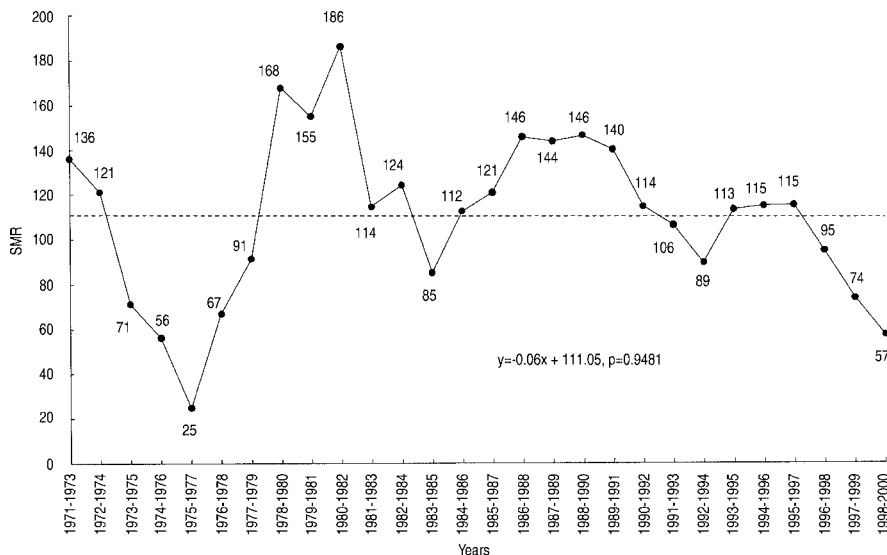


Fig. 1. Time trends of SMRs for male DM in BFD-endemic area for 3-year periods; 1971–2000; SMRs for each period are shown above points.

tality analysis is made. In the event of a death in Taiwan, the decedent’s family is required to obtain a death certificate from the hospital or local community clinic, which then must be submitted to the household registration office in order to cancel the decedent’s household registration. The death certificate is required to have the decedent’s body buried or cremated. Furthermore, the main cause of death must be recorded by physicians on all death certificates forwarded to the National Health Department, and this requirement has remained the same throughout the time periods of our study. Therefore the observed trends noted in this study are not considered

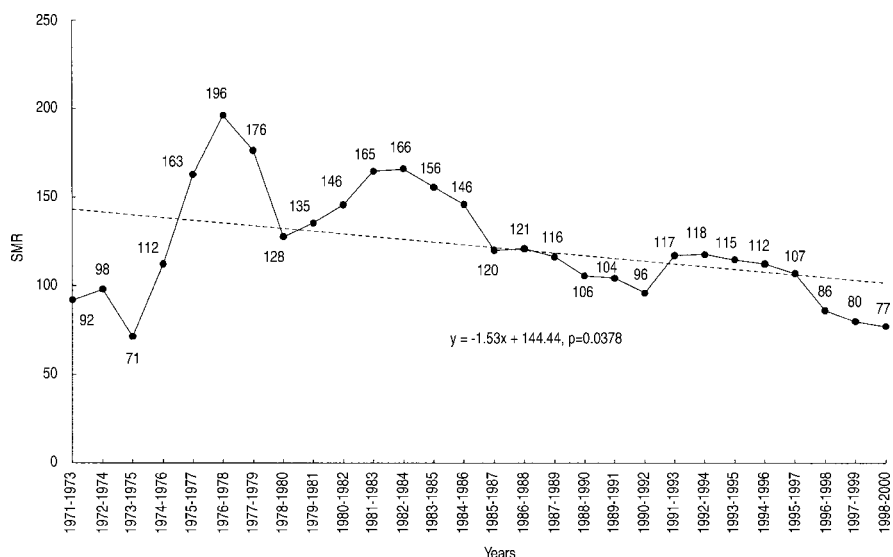


Fig. 2. Time trends of SMRs for female DM in BFD-endemic area for 3-year periods; 1971–2000; SMRs for each period are shown above points.

to be attributed to change in recording practices.

Several studies have demonstrated that DM was reported as the underlying cause in only 7% and as a contributing or “other” cause in approximately one-third of all death certificates.^{17–19} Therefore underestimation of mortality rates from DM is inevitable if vital statistic data is used.²⁰ However, there was no reason to expect that the underestimation of mortality rate from DM might have occurred differentially between the endemic study areas and the whole of Taiwan, and therefore this factor was not likely to have had a significant effect on the associations we observed.

Taiwan is a small island with a convenient communication network. It is believed that all DM cases in study areas have had access to medical care. Moreover, improvements in diagnosis or therapy may affect case fatality rates. Data are not available concerning improvement in case ascertainment or treatment over the study periods. However, it is unlikely that there was a differential in these factors between the endemic study areas and the whole of Taiwan, according to time period of diagnosis. Therefore, the observed trends were not likely to have been affected

significantly by changes in medical practice.

Obesity has been reported as a risk factor for DM in Taiwan.²¹ This factor was not taken into account due to the lack of available data on the prevalence rate of obesity in the study area. If the prevalence rate of obesity has declined slowly and progressively during the period studied, one would expect that this change would result in a reduction in DM death rates in the study area. However, it seems quite unlikely that changes in the prevalence rate of obesity would be correlated with changes in water supply system. We therefore believe that obesity should not have been a confounding factor in this study.

With respect to migration, lifestyle, and occupational exposure, most of the residents in the study area engaged in farming, fishery, and salt production and have lived there all their life.⁴ The dietary pattern of residents in the study area was not different from that of the general population in Taiwan. They even consume more vegetables, fiber, and complex carbohydrates than do residents of other socioeconomically better developed areas in Taiwan.⁴ The only significant difference in environment between the BFD-

endemic areas and other areas is the arsenic content of drinking water derived from artesian well water before 1975. The change in the water supply constituted a significant change in their lifestyle.

The mechanism through which inorganic arsenic would induce DM is not well understood. It has been proposed that arsenic could induce insulin-dependent and non-insulin-dependent diabetes, probably through increased oxidative stress.^{22,23} Furthermore, this increased arsenic-induced oxidative stress has been found to induce the development of insulin resistance and atherosclerosis,²⁴ mainly through the depletion of glutathione,²⁵ and the latter may be profound in hyperglycemia or diabetic states.²⁶

If the association between arsenic exposure and DM was causal, a significant reduction in DM mortality would be anticipated for both male and female residents. Our results, however, indicate that the reduction was restricted to women. Previous studies have found that women had a higher prevalence of DM than men in BFD endemic areas^{5,7} but that the reverse was true in nonendemic areas of Taiwan.^{7,27,28} These findings might suggest a hypothesis that women are more susceptible to arsenic exposure than are men. It is also possible that women might have drunk more local water than men and thus the impact of the cessation of consumption of the high arsenic well water was more important in women. The discrepancy between women and men also may result from the possibility that men are exposed to a greater number of other risk factors related to DM (such as higher body mass index and triglyceride concentrations) than are women in the BFD endemic area and, therefore, the SMRs for male DM did not decline gradually after the cessation of consumption of high-arsenic artesian well water.

In summary, this study shows that mortality from female DM declined gradually after the cessation of con-

sumption of artesian well water containing high amounts of arsenic. On the basis of the reversibility criterion, this finding suggests that the association between arsenic exposure and DM is likely to be causal for females but not in males.

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