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Arsenic Exposure and Prevalence of Diabetes Mellitus in Korean Adults

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It has been suggested that there is an association between environmental, low-level arsenic exposure and the risk of diabetes mellitus (DM), but little research has been conducted. Here, the glucose tolerance status and urinary creatinine adjusted total arsenic concentrations were analyzed in 3,602 subjects ≥ 20 yr of age who were registered for the Korea National Health and Nutrition Examination Survey, 2008-2009. Various demographic parameters were associated with urinary arsenic concentrations. After adjusting for these variables, urinary arsenic concentrations in subjects with DM were significantly higher than those in subjects with normal glucose tolerance and those with impaired fasting glucose ($P < 0.001$). Compared with the lowest quartile (< 70.7 μg/g creatinine), the odds ratios and 95% confidence intervals for DM were 1.11 (0.73-1.68), 1.42 (0.94-2.13), and 1.56 (1.03-2.36) for urinary arsenic concentrations of 70.7 to < 117.7, 117.7 to < 193.4, and ≥ 193.4 μg/g creatinine, respectively, following multivariate adjustment. Furthermore, the urinary total arsenic concentration was inversely associated with the insulin secretion index, HOMA2 %B ($\beta = -0.033$, $P = 0.032$). These findings suggest that arsenic exposure, possibly involving beta cell dysfunction, is associated with an increased risk of DM in the Korean population.

Key Words: Diabetes Mellitus; Arsenic; Arsenic Poisoning; Hyperglycemia; Blood Glucose; Insulin Resistance; Korea; KNHANES

INTRODUCTION

Chronic exposure to inorganic arsenic may be related to an increased risk of diabetes mellitus (DM). According to epidemiological studies conducted in endemic arsenic exposure areas such as Taiwan, Bangladesh, and Mexico, chronic exposure to high levels of arsenic is related to higher levels of glycated hemoglobin and DM risk (1-4). Specifically, chronic exposure via drinking water to inorganic arsenic at levels of 100 μg/L or higher is significantly related to DM risk (5, 6).

Chronic inorganic arsenic exposure has been shown to be related to DM risk even in general environmental areas where there is almost no possibility of high-level exposure. For example, the results of a study of National Health and Nutrition Examination Survey (NHANES) subjects showed that environmental, low-level arsenic exposure was related to DM risk (7). However, this study lacked generality in that it did not reflect subjects from areas other than the U.S and, furthermore, other studies did not find that low-level inorganic arsenic exposure was a distinct DM risk (8-13). In addition to the lack of generality and positive findings from other studies, there are few, if any, detailed studies of the mechanism by which chronic, low-dose arsenic exposure increases DM risk. Therefore, further research is necessary to determine whether or not there is an association between environmental, low-level arsenic exposure and DM risk in general populations in various parts of the world, and if so, which associated pathophysiology links insulin resistance and insulin secretory dysfunction.

In January 2011, the raw data of the Korea National Health and Nutrition Examination Survey (KNHANES) IV, conducted by the Korea Centers for Disease Control and Prevention, were released. In particular, the 2008 and 2009 KNHANES IV data include urinary total arsenic and blood heavy metal levels (14, 15). Other investigations based on the KNHANES 2008 data have recently reported an association between urinary total arsenic concentration and the prevalence of DM in Koreans, especially in females (16). However, it appears that the results of this study leave much room for further discussion in terms of study subjects, design, and analytic methods. Thus, this study utilized a nationally representative Korean population data from the 2008-2009 KNHANES IV to determine the relationship between environmental arsenic exposure and glucose tolerance status as well as the mechanism of insulin secretory dysfunction.

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MATERIALS AND METHODS

KNHANES IV

The KNHANES is a nationwide, population-based, and cross-sectionally designed health survey conducted by the Korea Centers for Disease Control and Prevention (14, 15). After the first KNHANES was performed in 1998, the second, third, and fourth surveys were conducted in 2001, 2005, and 2007-2009, respectively. KNHANES IV subjects were defined as households or individuals included in the 2005 Korean Population and Housing Census. Relevant households were selected randomly using stratified and multistage probability sampling. By assigning weights to each respondent, the sample for each year was the probability sample representing all parts of the country. Each sample had homogenous and independent characteristics, and all subjects in the surveys participated voluntarily and informed consent was obtained.

Study subjects

This study utilized the 2008 and 2009 KNHANES IV data, which included urine and blood heavy metal assays. Heavy metal sampling was performed on 2,000 subjects annually, comprising 10 subjects selected randomly from each survey unit according to age and gender. Urine samples were collected and subjected to a total arsenic concentration assay and whole blood samples were subjected to lead, mercury, cadmium, and manganese assays. Blood sampling was performed on 3,997 and urine sampling on 3,921 of a total of 4,000 subjects.

Among those subjected to the arsenic assay, patients with current chronic diseases that might have had an effect on arsenic exposure (n = 98), including active tuberculosis (n = 8), chronic obstructive pulmonary disease (n = 22), chronic kidney disease (n = 7), chronic liver disease (n = 32), and malignancy (n = 32), as well as subjects missing a chronic disease history (n = 6) were excluded. In addition, subjects missing demographic and clinical variables on the health interview and health examination, including smoking (n = 7), alcohol (n = 6), occupation (n = 21), education (n = 9), household income (n = 62), physical activity (n = 12), body mass index (n = 15), and glucose tolerance status (n = 109) were excluded. Thus, 3,602 were eligible for inclusion in the analysis.

Specimen collection and assay

Samples were collected after a fast of at least 8 hr. Clean midstream urine was collected for urinalysis. A trace element EDTA tube (BD; Franklin Lakes, NJ, USA) was used for blood sample collection. Urinary total arsenic concentrations were measured with a graphite furnace atomic absorption spectrometer (AAnalyst 600, Perkin Elmer; Finland) and specimens were immediately transferred to a central laboratory (NeoDIN Medical Institute; Seoul, Korea). To adjust for any effect of seafood intake (a source of organic arsenic) on arsenic concentration, blood mercury concentrations were included in the analyses (7).

The limit of detection for the arsenic concentration was 1.679 μg/L; the concentrations in all samples were higher than this value. The inter-assay coefficients of variation for the urinary arsenic assay were 2.5%-3.2% in KNHANES, 2008 samples and 2.3%-4.3% in KNHANES, 2009 samples. To correct for the effect of the difference in creatinine clearance among the subjects, urinary arsenic concentrations were expressed on a urinary creatinine basis. Blood mercury concentrations were measured using a gold amalgam method (DMA-80; Milestone, Italy). The limit of detection for the mercury concentration was 0.05 μg/L; the concentrations of all samples were higher than this value. The inter-assay coefficients of variation for the mercury assay were 1.1%-4.1% in KNHANES, 2008 samples and 1.2%-5.3% in KNHANES, 2009 samples.

Fasting plasma glucose (FPG) concentrations were measured using an automated analyzer (Hitachi Automatic Analyzer 7600; Hitachi, Tokyo, Japan) with an enzymatic assay (Pureauto SCHO-N, DAIICHI; Tokyo, Japan). Serum insulin concentrations were measured using a gamma counter (1470 Wizard, Perkin Elmer; Turku, Finland) and an immunoradiometric assay (Biosource; Nivelles, Belgium).

Demographic and clinical variables

To determine the differences according to demographic characteristics and urinary arsenic levels, the subjects were subdivided according to the classification of each variable.

Body mass index (BMI) was classified into: 1) < 18.5 kg/m^2, 2) 18.5-22.9 kg/m^2, 3) 23-24.9 kg/m^2, and 4) ≥ 25 kg/m^2; this was based on the diagnostic criteria of the Korean Society for the Study of Obesity (17). The 16 KNHANES residence areas were classified into: 1) urban areas; metropolitan cities such as Seoul, the capital city, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan, as well as metropolitan areas such as Gyeonggi province; and 2) rural areas; comprising Gangwon, Chungbuk, Chungnam, Jeonnam, Jeonbuk, Gyeongbuk, Gyeongnam, and Jeju provinces.

The physical activity of the subjects was categorized by investigating recreational physical activity over the previous week into: 1) none, no activity; 2) mild, > 30 min of walking more than 5 days per week; 3) moderate, > 30 min of moderate physical activity in which the subject was tired compared with an ordinary level or breathing slightly hard more than 5 days per week; and 4) vigorous physical activity, > 20 min of vigorous physical activity in which the subject was exhausted compared to an ordinary level or breathing hard more than 3 days per week. Current smokers were defined as those who had smoked more than five packs of cigarettes during their life and were smoking currently, and non-smokers were all others. Regular alcohol drinkers were those who drank alcohol currently more than once per

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month, and non-drinkers were all others.

Educational status was categorized as: 1) graduation from elementary school or lower, 2) graduation from middle school, 3) graduation from high school, and 4) graduation from college or higher. Occupation was divided into seven groups: 1) managers, professionals, technicians, and associated professionals, 2) clerical support workers, 3) service and sales workers, 4) skilled agricultural, forestry, and fishery workers, 5) craft and related trades workers, plant and machine operators, and assemblers, 6) elementary occupations, and 7) housewife, student, and unemployed. This categorization was based on the 6th Korean Standard Classification of Occupations from the Korean National Statistical Office created by following the International Standard Classification of Occupations of the International Labor Organization (18, 19).

Glucose tolerance status was divided into: normal glucose tolerance (NGT), defined as FPG < 100 mg/dL; impaired fasting glucose (IFG), defined as FPG 100-125 mg/dL; and DM, defined as FPG ≥ 126 mg/dL. This categorization was based on the diagnostic criteria of the American Diabetes Association (20). If subjects were confirmed to have DM by physicians, had used oral hypoglycemic agents (OHAs), or had taken insulin injections they were classified as having DM regardless of their fasting glucose level.

The insulin sensitivity and insulin secretion capacity of the subjects were assessed by means of FPG and fasting serum insulin. HOMA2 (Homeostasis of model assessment 2) %S and HOMA2 %B were utilized by employing the HOMA2 method, a computerized improvement on the standard HOMA method (21, 22). The HOMA2 method reflects insulin resistance (HOMA2 %S) and insulin secretion capacity (HOMA2 %B) in a more accurate fashion than did the previous HOMA method (22). To exclude the effects of medications, subjects who had taken OHAs or who had a history of insulin treatment (n = 176) were not analyzed by the HOMA2 method.

Statistical analysis

The differences in urinary total arsenic levels according to demographic and clinical characteristics and glucose tolerance status were investigated based on the health interview and health examination data of KNHANES IV. Additionally, the differences in the prevalence and risk of DM according to arsenic level were evaluated by subdividing the subjects by quartile of urinary arsenic concentration. Finally, the correlations of urinary arsenic concentration with fasting glucose, fasting insulin, HOMA2 %S, and HOMA2 %B indices were evaluated.

All data are presented as geometric means (GM) ± 95% CIs or as proportions (23). Predictive Analytics SoftWare (PASW; version 18.0, SPSS, Inc.; Chicago, IL, USA) was utilized for statistical analysis and data management. The differences in urinary arsenic concentration based on subject characteristics and on glucose tolerance subgroups were determined and the influence of all other significant variables was adjusted for using an analysis of covariance (ANCOVA). Linear-by-linear association analyses were performed to verify the significance of IFG and DM prevalence trend with respect to the quartile of the urinary arsenic concentration. To investigate the degree of DM risk based on urinary arsenic concentrations, odds ratios (OR) for the prevalence of DM were calculated using the lowest arsenic quartile subgroup as the standard and the effect of all other significant confounders was adjusted for using logistic regression. Testing for linear trends was performed for the coefficients of the continuous version of the arsenic quartile entered in the same models (24). To clarify the relationships between insulin sensitivity/secretion indices and urinary arsenic concentration, multiple linear regression models were used. Natural logarithmic transformation was used for skewed variables. P values < 0.05 were considered to indicate significance.

Ethics statement

This study was approved by the institutional review board of the Kyung Hee University Hospital (IRB No. KMC IRB 1220-05). Because this study analyzed publicly available data, informed consents were waived.

RESULTS

Differences in urinary arsenic according to demographic characteristics

The creatinine adjusted urinary total arsenic levels of the subjects ranged from 6.1 μg/g creatinine to 2,990.2 μg/g creatinine (median, 117.7 μg/g creatinine). The urinary arsenic concentrations of the subjects were significantly different according to demographic characteristics (Table 1). Male subjects (49.2%) exhibited arsenic levels significantly lower than those of females. Subjects aged 19-39, 40-59, and > 60 yr accounted for 40.1%, 40.1%, and 19.7% of all subjects, respectively, and the older age group exhibited significantly higher arsenic concentrations compared to the younger age groups. The urinary arsenic concentration was significantly higher in rural areas than in urban areas. The arsenic level of current smokers was lower than that of non-smokers, whereas the arsenic level of regular drinkers was significantly higher than that of non-drinkers. The difference in urinary arsenic concentrations according to occupation was also significant. The concentration in clerical support workers was significantly lower than among subjects in other occupations, with the exception of managers, professionals, technicians, and associate professionals. When subjects were compared according to the quartile of their mercury concentration, the urinary arsenic concentration was lowest in the lowest quartile and increased significantly as blood mercury concentration increased. No difference in arsenic concentra-

Table 1. Urinary total arsenic concentrations of study subjects according to demographic characteristics and glucose tolerance status adjusted for all other significant variables

Variables	No. (%)	Total arsenic (μg/g creatinine)	*Post hoc P*	Adjusted *P**
Gender				
Male	1,772 (49.2)	93.8 (90.6-97.0)	-	< 0.001
Female	1,830 (50.6)	140.1 (135.5-144.9)	-	
Age (yr)				
20-39	1,446 (40.1)	90.6 (87.1-94.1)	Reference	< 0.001
40-59	1,445 (40.1)	128.3 (123.8-132.8)	< 0.001	
≥ 60	711 (19.7)	157.6 (148.4-167.3)	< 0.001	
BMI (kg/m^2)				
< 18.5	163 (4.5)	112.6 (101.9-124.3)	Reference	0.088
18.5-22.9	1,395 (38.7)	119.5 (115.4-123.7)	1.000	
23-24.9	918 (25.5)	113.1 (108.3-118.0)	1.000	
≥ 25	1,126 (31.3)	112.3 (107.9-116.8)	1.000	
Resident area				
Urban area	2,371 (65.8)	113.1 (110.2-115.9)	-	0.007
Rural area	1,231 (34.2)	120.5 (115.9-125.5)	-	
Physical activity				
None	1,499	117.0 (113.2-120.9)	Reference	0.181
Mild	1,099	116.9 (112.4-121.6)	1.000	
Moderate	341	109.3 (101.8-117.2)	0.523	
Vigorous	663	111.7 (106.3-117.6)	0.825	
Smoking				
No smoker	2,705 (75.1)	119.2 (116.3-122.4)	-	< 0.001
Current smoker	897 (24.9)	104.0 (99.1-109.1)	-	
Alcohol				
No drinker	1,519 (42.2)	111.8 (108.0-115.7)	-	0.030
Regular drinker	2,083 (57.8)	117.8 (114.4-121.4)	-	
Education				
Elementary school or lower	782 (21.7)	122.2 (115.2-129.5)	Reference	0.134
Middle school	413 (11.5)	118.9 (111.1-127.1)	1.000	
High school	1,351 (37.5)	113.8 (109.7-117.9)	0.315	
College or higher	1,056 (29.3)	111.4 (106.7-116.4)	0.143	
Occupation†				
Group 1	459 (12.7)	114.6 (107.6-122.0)	0.053	< 0.001
Group 2	302 (8.4)	99.4 (92.4-106.9)	Reference	
Group 3	475 (13.2)	117.1 (110.5-124.1)	0.010	
Group 4	248 (6.9)	127.7 (116.2-140.5)	0.001	
Group 5	401 (11.1)	131.9 (123.2-141.2)	< 0.001	
Group 6	339 (9.4)	122.1 (113.6-131.4)	0.003	
Group 7	1,378 (38.3)	111.1 (107.1-115.2)	0.181	
Serum mercury (μg/L)				
Quartile 1 (< 3.1)	900 (25.0)	85.7 (82.0-89.6)	Reference	< 0.001
Quartile 2 (3.1 to < 4.3)	901 (25.0)	109.6 (105.0-114.4)	< 0.001	
Quartile 3 (4.3 to < 6.4)	900 (25.0)	116.9 (111.8-122.1)	< 0.001	
Quartile 4 (≥ 6.4)	901 (25.0)	160.8 (153.7-168.2)	< 0.001	
Glucose tolerance status				
Normal glucose tolerance	2,621 (72.8)	112.8 (110.1-115.8)	Reference	< 0.001
Impaired fasting glucose	672 (18.7)	117.6 (111.7-123.7)	0.506	
Diabetes mellitus	309 (8.6)	133.2 (123.1-144.0)	< 0.001	
Total	3,602 (100.0)	-		-

by ANCOVA. Total urinary arsenic concentrations expressed as geometric mean and 95% confidence intervals. *Adjusted for all other significant variables. †Occupation group refers to the KSCO-6 classification. Group 1 indicates managers, professionals, technicians and associate professionals; Group 2, clerical support workers; Group 3, service and sales workers; Group 4, skilled agricultural, forestry and fishery workers; Group 5, craft and related trades workers, plant and machine operators, and assemblers; Group 6, elementary occupations; Group 7, housewife, student, and unemployed.

tion according to BMI, physical activity, or education was identified.

Differences in urinary arsenic according to glucose tolerance

Subjects were classified by glucose tolerance and 8.6%, 18.7%, and 72.8% were diagnosed with DM, IFG, and NGT, respectively (Fig. 1). The difference between NGT and IFG was not significant, but the urinary arsenic level of subjects with DM was significantly higher than that of subjects with NGT and IFG. Even after OHAs and insulin users had been excluded from the pool of subjects with DM, the results were unchanged (data not shown).

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Difference in DM risk based on urinary arsenic concentration

The prevalences of DM and IFG were compared according to the quartiles of urinary arsenic concentration. As the arsenic concentration increased, the IFG prevalence increased to 15.4%, 18.2%, 19.8%, and 21.2% and the DM prevalence to 4.8%, 7.1%, 9.9%, and 12.6% (Fig. 2) among quartiles. The increases in the IFG and DM prevalences were significant. When the difference in DM risk based on urinary arsenic concentration was investigated, the OR for the 70.7 to 117.7 μg/g creatinine urinary arsenic subgroup compared with the lowest quartile (< 70.68 μg/g creatinine) was 1.11 (95% CI, 0.73-1.68) and the OR for the 117.7 to 193.4 μg/g creatinine subgroup was 1.42 (95% CI, 0.94-2.13) after multivariate adjustment (Table 2). The OR for the ≥ 193.4 μg/g creatinine subgroup was 1.56 (95% CI, 1.03-2.36) indicating that the risks of DM were significantly greater in these subgroups. Moreover, the ORs for DM had significant linear trends when compared by arsenic quartiles. The ORs of the IFG were not significant (data not shown).

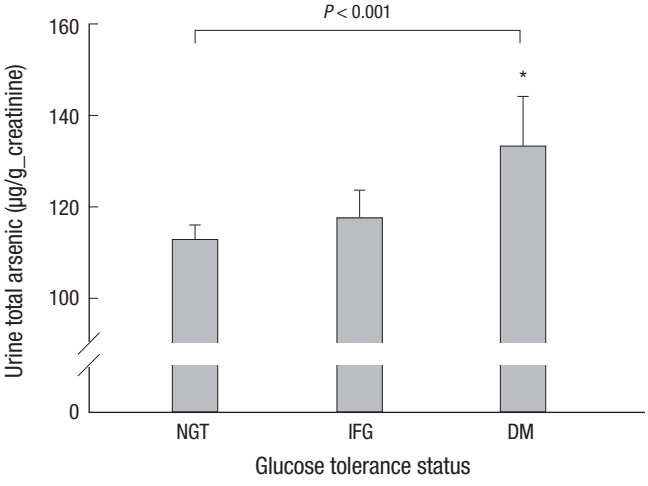

Fig. 1. Urinary total arsenic concentrations according to glucose tolerance status adjusted for all other significant variables. ANCOVA. Geometric mean with 95% confidence interval. *P < 0.01 by *post-hoc* analysis.

Correlation of urinary arsenic concentration with insulin sensitivity/secretion indices

The correlations of FPG, fasting serum insulin, HOMA2 %S, and HOMA2 %B with urinary arsenic in drug-naïve subjects were determined (Table 3). In multivariate regression analyses including potential confounders, urinary total arsenic was inversely associated with HOMA2 %B, the index of insulin secretion capacity. Fasting insulin had a weakly negative association with urinary arsenic, albeit non-significantly. Inclusion of subjects with a history of OHA or insulin use in the analysis resulted in no changes in significance (data not shown).

DISCUSSION

Humans are exposed to two types of arsenic compounds: organic and inorganic. Organic arsenic compounds are known to be nontoxic since they are not metabolized and are excreted rapidly (5), whereas inorganic arsenic compounds are highly toxic and have carcinogenic effects in humans (25). Most organic arsenic exposure is due to seafood intake, while inorganic arsenic exposure occurs via contaminated water and food (26). Recently, rice intake has been shown to be related to inorganic

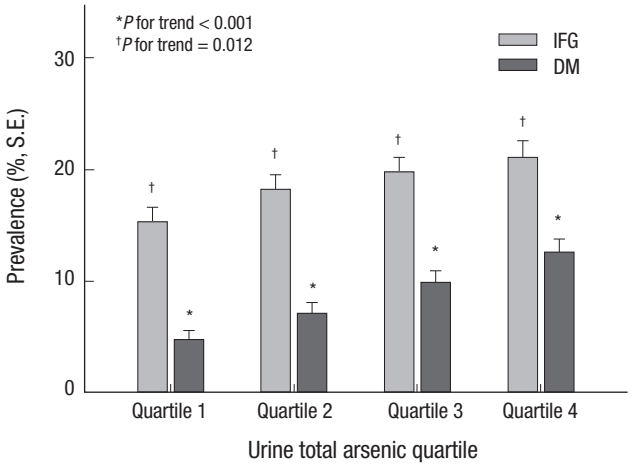

Fig. 2. Prevalence of IFG and DM according to total urinary arsenic concentration quartile. P for trend by linear-by-linear association.

Table 2. Adjusted ORs of study subjects with DM according to urinary total arsenic concentration

	Total arsenic concentration (μg/g creatinine)							
	Quartile 1 (< 70.7)	Quartile 2 (70.7 to < 117.7)	*P*	Quartile 3 (117.7 to < 193.4)	*P*	Quartile 4 (≥ 193.4)	*P*	*P* for trend*
DM								
Model 1†	Reference	1.08 (0.72-1.64)	0.708	1.35 (0.91-2.00)	0.140	1.45 (0.98-2.15)	0.061	0.028
Model 2‡	Reference	1.11 (0.73-1.68)	0.626	1.43 (0.96-2.12)	0.082	1.57 (1.06-2.34)	0.024	0.009
Model 3§	Reference	1.11 (0.73-1.68)	0.640	1.42 (0.94-2.13)	0.092	1.56 (1.03-2.36)	0.036	0.015

By logistic regression analysis. *Test for linear trend was performed for the coefficients of the continuous version of arsenic quartile entered in the same models; †Model 1 is shown as odds ratio (OR) and 95% confidence interval (CI); adjusted for sex (male or female), age (continuous), and residence area (urban or rural); ‡Model 2 is shown as OR (95% CI); further adjusted for smoking (current smoker or not), alcohol (current drinker or not) and occupation (by KSCO-6 classification); §Model 3 is shown as OR (95% CI); further adjusted for serum mercury level (log-transformed).

Table 3. Adjusted regression coefficients of fasting glucose, fasting insulin, HOMA2 %S, and HOMA2 %B with log-transformed urinary total arsenic in NGT, IFG, and drug-naive DM subjects

	Model 1*		Model 2†		Model 3‡	
	Standardized β	*P*	Standardized β	*P*	Standardized β	*P*
Fasting glucose	0.041	0.024	0.036	0.048	0.019	0.326
Fasting insulin§	-0.015	0.409	-0.003	0.879	-0.035	0.077
HOMA2 %B	-0.046	0.011	-0.029	0.103	-0.040	0.032
HOMA2 %S	0.009	0.615	-0.001	0.951	0.031	0.123

By multiple linear regression analysis. *Model 1: adjusted for sex (male or female), age (continuous), and residence area (urban or rural); †Model 2: further adjusted for smoking (current smoker or not), alcohol (current drinker or not) and occupation (by KSCO-6 classification); ‡Model 3: further adjusted for serum mercury level (log-transformed); §Log-transformed. NGT, normal glucose tolerance; IFG, impaired fasting glucose; DM, diabetes mellitus.

arsenic exposure (27, 28). In addition, mineral extraction, processing wastes, poultry, and swine feed additives are also known sources of manmade arsenic exposure (29, 30).

Epidemiological studies in occupational settings or in endemic areas in Taiwan, Bangladesh, and Mexico have shown that a high level of inorganic arsenic in drinking water is correlated with a risk of type 2 DM (1-6). Even in areas in which there is almost no possibility of high-level exposure, exposure to low-level arsenic may occur, and glucose metabolism can be affected. However, controversy regarding the correlation between low-level environmental inorganic arsenic exposure and the risk of DM remains. In a case control study in Mexico, the ORs of DM in groups with a total urinary arsenic level of 63.5-104 μg/g creatinine and > 104 μg/g creatinine were 2.16 (95% CI, 1.23-3.79) and 2.84 (95% CI, 1.64-4.92), respectively (3). In a cross-sectional study of the US NHANES subjects, the OR of DM in the 80th percentile for urinary total arsenic was 3.58 (95% CI, 1.18-10.83) (7). However, in another US study, the ORs of DM for subgroups with a urinary arsenic concentration of 2-10 μg/L and > 10 μg/L to a urinary arsenic < 2 μg/L subgroup were 1.4 (95% CI, 0.8-2.3) and 1.1 (95% CI, 0.5-2.2), respectively, and were not significant (11). In a recent cross-sectional study in Bangladesh, no significant association between arsenic exposure via drinking water and the risk of DM was found (13). The heterogeneity of this association in previous studies may be due to differences in the many relevant factors, such as study design, study subjects, arsenic measurement, statistical analyses, and so on. To reach more definite conclusions, future studies should be performed within broader areas, with more subjects, and using more detailed analytic methods.

In this study, the correlation between arsenic exposure and the risk of DM was investigated using KNHANES data, which represents the general population of Korea. Additionally, the pathophysiology by which arsenic exposure influences the risk of DM was verified using the HOMA2 model, which allows for a relatively accurate estimation of the insulin secretion and insulin sensitivity of the subjects (21, 22). Notably, the absolute urinary total arsenic concentration is higher in Koreans than in Westerners because Koreans consume more rice and seafood (27). Hence, in this study, blood mercury levels, which are known to have a strong correlation with seafood consumption, were also analyzed to exclude as much as possible the effect of organic arsenic (7).

The findings suggest that several diverse demographic characteristics may influence urinary total arsenic concentration in Korean adults. The urinary total arsenic concentration was significantly higher in females, the elderly, residents of urban areas, non-smokers, regular drinkers, and the high blood mercury subgroup. Significant differences among occupations were also found. Overall, this result is similar to that of a previous epidemiological study of the general population (7).

The most important finding of this study was that the total urinary arsenic concentration of DM subjects was significantly higher than that of NGT and IFG subjects even after blood mercury concentration, an indicator of seafood intake, had been corrected for. The prevalence of IFG and DM among subjects was also significantly greater according to the quartiles of urinary arsenic concentration. Logistic regression analysis showed that the OR of DM within the highest urinary arsenic quartile was 1.56, which was significantly greater. In addition, the ORs exhibited significant linear trends by arsenic quartiles. This result demonstrates clearly that environmental low-level arsenic exposure may result in an abnormal glucose tolerance in the general Korean population.

Additionally, we indirectly estimated the effect of arsenic status on the pathophysiology of DM in Koreans. A multiple linear regression analysis showed that urinary total arsenic concentration had a significant negative correlation with HOMA2 %B, an insulin secretion capacity index, and a weak association with fasting serum insulin. This indicates that DM risk due to arsenic exposure is related mainly to beta cell dysfunction, rather than insulin resistance, in Koreans. According to previous experimental models, arsenic exposure inhibits insulin-dependent glucose uptake, causes insulin secretion impairment by repressing beta cell insulin signaling and transcription, and brings about an increased risk of DM by modifying the expression of genes related to insulin resistance (31, 32). However, the effects of low-level exposure cannot be explained by these experimental models as they used relatively high arsenic concentrations. Because the mechanism underlying the increased risk of DM

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following low-dose arsenic exposure has not been investigated in previous studies, the current results may facilitate determination of the mechanism by which environmental arsenic exposure increases the risk of DM in the general population. However, even though a significant negative correlation was found between HOMA2 %B and urinary arsenic concentration, the regression coefficient was not sufficient to indicate a dominant role in glucose metabolism. In fact, no significant correlation in fasting blood glucose was found in the regression analyses. In addition, it should be taken into account that various factors were not corrected for in this study, including the nutritional status and individual variability to detoxification of the subjects.

We believe that this study has a strength compared to a previous report (16). First, more extensive analyses with many subjects were able to be conducted because we utilized all available arsenic-related data in the KNHANES IV. Using these analyses, more consistent and gender-nonbiased results were generated. Second, because this study included almost all aspects of the health interviews and health examination data from the KNHANES IV in the analyses, it was possible to adjust as much as possible for the influences of demographic characteristics. Third, because the nutritional surveys and blood sampling in the KNHANES IV were conducted on different days, it is likely that the nutritional survey was not entirely appropriate in terms of adjusting for the effects of seafood intake in the KNHANES IV data. Instead of a nutritional survey, we utilized blood mercury levels—which are known to be highly correlated with seafood intake—generating more convincing results (7). Finally, the use of HOMA2 indices as indicators of insulin sensitivity and insulin secretion could explain the putative mechanism of the association between arsenic exposure and glucose metabolism.

This study has some limitations. First, as KNHANES IV was a cross-sectional study, the causal relationship between urinary arsenic status and glucose tolerance status is unclear. Second, the effect of inorganic arsenic concentrations was not analyzed directly, since the total urinary arsenic concentration was measured. Third, the HOMA2 method used is not a gold standard method of measuring insulin secretion or insulin sensitivity. Despite these limitations, the results are meaningful because they demonstrate a significant correlation between environmental arsenic exposure and DM risk as well as clarify important characteristics of arsenic exposure status in Koreans using a large number of subjects that are representative of the entire Korean population.

In conclusion, diverse demographic characteristics influence urinary arsenic status in Korean adults. Additionally, high urinary arsenic concentrations are significantly related to DM risk and the effect of arsenic on glucose metabolism is closely associated with beta cell dysfunction in the Korean population. Future large-scale longitudinal studies that overcome the limitations of the current study will facilitate a more detailed view of the pathophysiological role of arsenic in glucose metabolism.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

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