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Environmental Arsenic Exposure and Diabetes

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TYPE 2 DIABETES MELLITUS EMERGED AS A PANDEMIC in the later half of the 20th century. In the United States alone, diabetes affects an estimated 7.8% of the US population (24 million individuals) and its prevalence is projected to almost double in the next 25 years.^{1,2} The complications associated with diabetes including cardiovascular disease, retinopathy, nephropathy, neuropathy, and lower limb amputation profoundly affect the quality of life and contribute to the high morbidity and mortality associated with this disease. Diabetes is ranked as the seventh leading cause of death in the United States in 2006²; the economic costs of diabetes are also high. Approximately \$1 of every \$10 in US health care expenditures can be attributed to the direct costs associated with diabetes.³ When indirect costs to caregivers are included, it is estimated that the annual cost of diabetes in the United States is \$174 billion.³

Characterized by a combination of deficient insulin secretion and a diminished response to insulin at the target tissue, which can progress to hyperglycemia, the risk of type 2 diabetes increases with age, obesity, and sedentary lifestyle.⁴ Clinical trials have shown that lifestyle modification including weight reduction and increased physical activity can reduce the prevalence of type 2 diabetes by as much as 58%,⁵ and now these 2 behavioral issues have become the cornerstone of diabetes prevention programs.

Yet the etiology of type 2 diabetes remains poorly understood and the role of environmental pollutants, specifically arsenic, in diabetogenesis has received little attention by the medical community. This is somewhat surprising because arsenic exposure has been linked to type 2 diabetes since 1950 when a case report documented a patient developing type 2 diabetes after receiving intravenous arsenical treatment for sexually transmitted diseases.⁶ However, research efforts on the role of arsenic in diabetogenesis did not intensify until population-based epidemiologic studies published in the 1990s from Taiwan⁷⁻⁹ and Bangladesh¹⁰ demonstrated that chronic exposure to high levels of arsenic from

drinking water is associated with a higher prevalence of type 2 diabetes.

While the findings of these studies were consistent and indicated a dose-response relationship between chronic arsenic exposure and type 2 diabetes, these populations were considered somewhat unique. A proportion of the populations from Taiwan and Bangladesh may have been malnourished and many of the individuals displayed other symptoms of chronic arsenic toxicity including hypertension and cardiovascular disease—-independent risk factors for type 2 diabetes. Also, extrapolating from chronic high-dose effects to chronic low-dose effects of arsenic exposure on type 2 diabetes was debatable since many of the drinking water wells in Taiwan and Bangladesh contained several hundred micrograms of arsenic per liter.^{7,9,10}

In this month's issue of JAMA, Navas-Acien et al¹¹ are the first authors to report a positive association between low-level arsenic exposure and the prevalence of type 2 diabetes in the United States. Using newly available urinary arsenic data from National Health and Nutrition Examination Survey, a population-based survey conducted by the Centers for Disease Control and Prevention that collects information on the health and nutrition of the US population, the authors report a 3.6-fold increase in the odds of diabetes for participants with the highest total urinary arsenic concentrations as compared with participants with the lowest total urinary arsenic concentrations.¹¹

There are several noteworthy points to this analysis. First, arsenic exposure is ascertained at an individual level using total urinary arsenic. The authors have taken considerable effort to isolate the effect of inorganic arsenic by controlling for nontoxic arsenic species that could influence urinary arsenic levels from the consumption of seaweed, fish, or shellfish. Second, the arsenic exposures reported in this study may be less than the current US Environmental Protection Agency reference dose level of 0.3 µg per kilogram of body weight per day.¹² Using standard reverse dosimetry that assumes an individual is in equilibrium with the environment and that assumes all ingested arsenic is excreted and 1 liter of urine is produced per day, a 70-kg adult with

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See also p 814.

a total urinary arsenic concentration of 7.1 µg/L¹¹ would have ingested a dose approximately equivalent to 0.1 µg per kilogram of body weight per day, which is 3 times lower than the US Environmental Protection Agency reference dose.

There are also several caveats that must be considered when using total urinary arsenic as the exposure metric. Urinary arsenic is a biomarker of short-term exposure with a half-life of approximately 3 days,¹³ which makes it difficult to ascertain historical exposures that may be more relevant for the pathogenesis of type 2 diabetes. Since arsenic toxicity is a function of duration of exposure as well as dose, this is an important limitation of this analysis. Also, type 2 diabetes is a complex metabolic disorder characterized by abnormalities in carbohydrate, lipid, and protein metabolism as well as kidney function. If individuals with diabetes also have altered xenobiotic metabolism and excretion, the utility of using urinary arsenic concentrations as the biomarker of exposure could be limited.

This limitation extends to other studies that also have reported higher levels of arsenic and other metals in the hair, blood, and urine of individuals with diabetes compared with individuals without diabetes.^{14,15} Thus, future epidemiologic studies should incorporate detailed environmental exposure assessment measurements as well as biomarkers of exposure when examining the relationship between xenobiotics and metabolic disorders.

In addition to the epidemiological evidence supporting an association between arsenic and type 2 diabetes, it is also important to examine the toxicological data. Although it is most commonly recognized as a potent human carcinogen,¹⁶ inorganic arsenic is a pleuripotent toxicant. Animal studies show that arsenic disturbs glucose production in the liver and decreases insulin secretion and synthesis in pancreatic β cells.¹⁷ In addition, arsenic exposure causes hyperglycemia, hyperinsulemia, and low-insulin sensitivity in rats, which is consistent with insulin resistance observed in type 2 diabetes.¹⁸

Stemming the pandemic of type 2 diabetes is a public health priority and will require a multifaceted approach. This must include improving the understanding of the etiology of diabetes and identifying modifiable factors that can be incorporated into prevention strategies. To date, this approach has focused on medication and lifestyle modification, but the role of environmental exposures must also be considered. While many questions remain about the role of

arsenic in diabetogenesis, they can only be answered by additional research. In the meantime, arsenic exposure from drinking water is a widespread environmental pollutant that affects millions of individuals around the world.¹⁶

It is prudent to minimize arsenic exposure while its effect on metabolic diseases continues to be researched.

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