

## A Complex Relationship: Dietary Folate, Arsenic Metabolism, and Insulin Resistance in Mice

Silke Schmidt

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More than 144 million people worldwide are believed to drink water with inorganic arsenic (iAs) concentrations exceeding the World Health Organization guideline of 10 ppb.<sup>1</sup> Consumption of drinking water with high levels of iAs—more than 100 ppb—has been associated with numerous adverse health outcomes in humans,<sup>2</sup> including diabetes.<sup>3,4</sup> A recent study<sup>5</sup> published in *Environmental Health Perspectives* highlights the potential complexity of the iAs–diabetes relationship: Investigators reported that, under some conditions, dietary folate may modify both iAs metabolism and diabetes-related outcomes in mice.

Previous research and known biochemical processes motivated the animal experiments. Several studies have suggested that the way iAs is metabolized may influence the associated health outcomes, including type 2 diabetes.<sup>6,7,8</sup> Some of the first evidence<sup>9</sup> that folate supplementation may increase the efficiency of human iAs metabolism came from Bangladesh, where exposure to arsenic-contaminated drinking water is much more common than in the United States.

In humans and some animal species, iAs is metabolized in multiple methylation steps. The synthesis of an important methyl donor for these reactions requires folate, an essential micronutrient.<sup>10,11</sup> The enzyme arsenic (+3 oxidation state) methyltransferase (AS3MT) catalyzes iAs methylation.<sup>12</sup> “Since we wanted to test whether the influence of folate varies by iAs metabolic efficiency, we used wild-type strains and *As3mt*-knockout mice with a reduced ability to detoxify iAs,” says Madelyn Huang, a postdoctoral fellow at the National Toxicology Program and first author of the new study. “We also compared the same iAs exposure in male and female animals on a low-fat and high-fat diet.”

In their study design, the researchers varied four factors: genetic background (wild-type vs. knockout), folate intake (0.2 mg/kg vs. 10 mg/kg), iAs in drinking water (0 ppb vs. 100 ppb), and dietary fat content. To minimize background dietary iAs, the mice received a purified low-fat diet. After 24 weeks, all the animals were switched to a high-fat diet to see if the added metabolic stress of an obesogenic regimen would alter the separate and combined effects of iAs and folate.



Exposure to potentially unsafe levels of iAs in drinking water is a problem for more than 144 million people worldwide. Bangladesh, India, the United States, and China are thought to have the largest populations of people exposed to concentrations above the World Health Organization guideline of 10 ppb.<sup>1</sup> In parts of these and other countries, drinking-water levels of iAs far exceed that guideline. Image: © iStockphoto/Tarzan9280.

Consistent with a previous study by members of this group,<sup>13</sup> *As3mt*-knockout mice were more likely than wild-type mice to become obese and develop insulin resistance, regardless of iAs exposure. The study also generated two novel findings: “Only obese and folate-deficient wild-type mice, male and female, that were exposed to arsenic developed insulin resistance,” says study leader Miroslav Stýblo, a professor of nutrition at the University of North Carolina at Chapel Hill. “But high folate intake, which rescued this phenotype [i.e., reversed insulin resistance] in both sexes, modified iAs metabolism only in female mice.”

These sex-specific effects are worth pursuing, according to Brandon Pierce, an associate professor of public health sciences at the University of Chicago who was not involved in the study. “In prior studies of humans, we have observed sex differences related to arsenic metabolism and arsenic-related disease risks, but the reasons for these differences are not well understood,” he says.

Pierce and colleagues are conducting several human studies in Bangladesh. Although these studies include only a small number of obese individuals, they are yielding evidence that diet may modify the risk of arsenic-induced skin lesions.<sup>14</sup> This finding, Pierce says, is consistent with the new study’s evidence for a potential interaction between iAs exposure and dietary factors.

Ana Navas-Acien, a professor of environmental health sciences at Columbia University and also not involved in the study, notes similarities with other studies. “In our human population,<sup>15</sup> the combination of arsenic exposure, low folate intake, and a fatty diet increased the risk of diabetes,” she says. “And I think one of [the new] study’s most important findings is that the *As3mt*-knockout mice were more obese under almost all conditions. This suggests that human AS3MT may play an important role in fat accumulation.”

Although it is possible that folate influences insulin resistance via iAs metabolism, Stýblo notes that other mechanisms cannot be ruled out. “Folate may have a larger systemic effect, perhaps involving changes in DNA methylation patterns for genes involved in glucose metabolism,” he says. “More work is needed to understand the role of both iAs and folate in the development of diabetes and other metabolic diseases.”

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**Silke Schmidt**, PhD, writes about science, health, and the environment from Madison, Wisconsin.

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