Doctoral Dissertation Defense

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THE USE OF METABOLOMIC PROFILING TO ELUCIDATE MECHANISMS UNDERLYING ARSENIC-ASSOCIATED DIABETES

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Arsenic is a naturally occurring metalloid that is associated with numerous health effects. More than 100 million individuals are exposed globally to high levels of arsenic chronically through contaminated drinking water sources. Studies have shown these individuals are more likely to develop Diabetes Mellitus (DM). At present, the National Toxicology Program has classified chronic exposure to arsenic above 150 ug/L as a probable diabtogen. Furthermore, more recent epidemiological studies have highlighted that chronic arsenic exposure above 150 ug/L maybe associated with DM. While *in vitro* and *in vivo* studies have elucidated possible mechanisms by which arsenic induces diabetes, it is still unclear which of these mechanisms is fully relevant to humans. Metabolomic profiling could help provide key insights into metabolic alterations that occur in individuals exposed to arsenic that lead to diabetes. As metabolomics is an emerging field profiling both diabetic and non-diabetic individuals chronically exposed to arsenic could provide insight into metabolic alterations associated with chronic arsenic exposure, as well as insight into which of these alterations are associated with the development of diabetes.

The goal of this research was to identify metabolites associated with alterations in associated with arsenic exposure in diabetic and non-diabetic individuals in Chihuahua, Mexico. Using 492 unique metabolites in urine and plasma through an untargeted metabolomic screening, we assessed the relationship between these metabolites total urinary arsenic (U-tAs), a commonly used measure of arsenic exposure, arsenic metabolism, as measured through speciated urinary arsenicals, and genotype of Arsenic +3 oxidation state methyltransferase (*AS3MT*), the main enzyme responsible for arsenic metabolism. We demonstrated that the identified metabolites are associated with alterations of key metabolic pathways including glucose metabolism, amino acid metabolism and vitamin B metabolism in association with arsenic exposure, arsenic metabolism and genotype of *AS3MT* in both diabetic and non-diabetic subjects. Many of the identified metabolites are associated with enzymes and metabolic pathways associated with the development of diabetes. Taken together, our research increases knowledge of mechanistic associations between arsenic-associated diabetes in humans.

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