ARSENIC
The Silent Toxin That Keeps On Giving

TEXAS BIOMEDICAL RESEARCH INSTITUTE
HEALTH STARTS WITH SCIENCE

Transformation of Original Research Article

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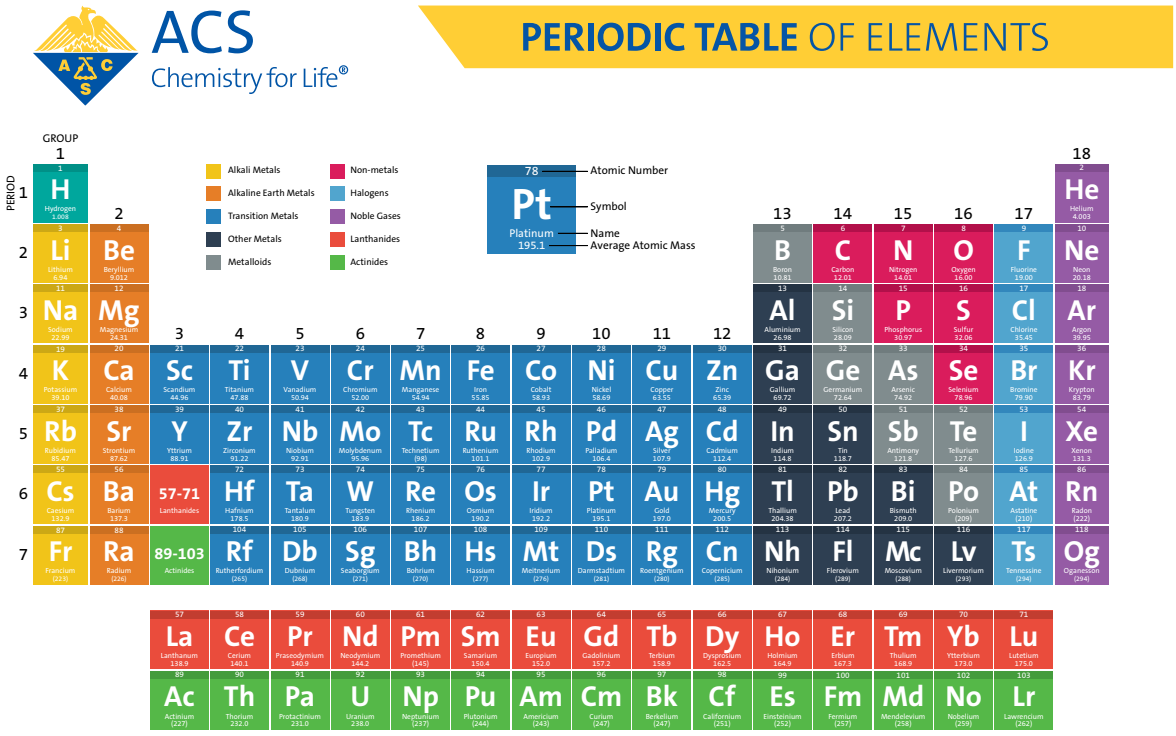
ABSTRACT

Exposure to low levels of ***arsenic (As)*** has been shown to increase the chronic diseases, such as type 2 diabetes (T2D), in American Indian communities. In this study, scientists sought to determine if the rate of type 2 diabetes in American Indian adults could be connected to their mothers' exposure to low to moderate levels of arsenic during pregnancy. Through data from the long-running Strong Heart Study (SHS), scientists studied mothers and their adult offspring to determine if a methyl group structure (CH_3) found on maternal DNA contributes to insulin-resistance in the adult offspring. When a methyl group attaches to DNA, it is called ***methylation (meth-ill-LAY-shun)***. The presence of As leads to DNA methylation (DNAm). Evidence indicates there is a relationship between the methylation of maternal DNA caused by exposure to arsenic during pregnancy and insulin resistance in their adult-offspring.

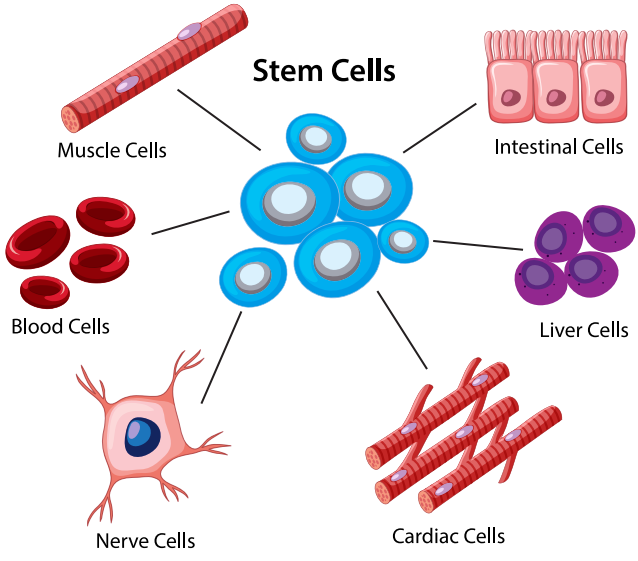
BACKGROUND

Epigenetics (ep-ah-geh-NEH-tics) is the study of how changes in gene expression affects the phenotype which is the physical appearance of an individual, but does not change the DNA sequence. Gene expression refers to when genes are active or not active. Changes to when genes are active or not active can negatively affect the body's metabolism. These changes in gene expression result from interactions between DNA strands. Although the DNA itself is not changed, epigenetic changes in gene expression can be inherited from one generation to the next. Epigenetic changes can also be influenced by environmental factors such as diet, stress, and exposure to toxins, such as arsenic.

Arsenic is a ***metalloid (MET-ah-loyd)***. Metalloids occur naturally in small amounts and are found in rocks, soil, water, and air. In large amounts, arsenic can be poisonous and even fatal. When arsenic is combined with other elements, it is stable and relatively harmless. However, when not chemically bound to another element, arsenic is highly toxic. Arsenic is considered to be a major global health concern due to its harmful effects on the human population.



During pregnancy, the mother's uterus develops a temporary organ called the ***placenta (plah-SEN-tah)***. The placenta is made of vascular tissue (lots of blood vessels) where the mother's circulatory system comes in close contact with the circulatory system of the developing fetus. Through diffusion, the placenta transfers nutrients and oxygen (O_2) from the mother to the fetus. Waste products, such as carbon dioxide (CO_2), move from the fetus through the placenta and into the mother's circulatory system to be removed. The placenta also protects the fetus by creating a barrier which protects the developing fetus from most toxins. However, arsenic is able to ***diffuse*** (move) through the placenta which may negatively affect fetal development. As the fetus develops, specialized cells called ***stem cells*** rapidly divide and ***differentiate (diff-er-EN-she-ate)***. When cells differentiate, it means they are becoming specific types of cells which come together to form unique tissues. Tissues then combine to form organs which create body systems, like the skeletal system which provides structure or the nervous system which controls movement and reactions.



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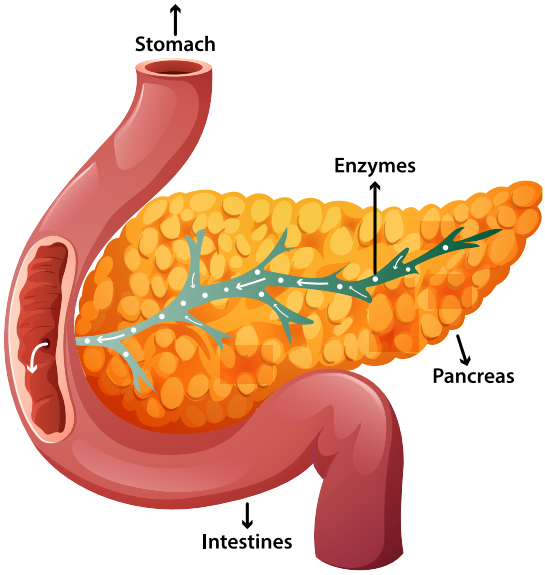
During the first trimester of pregnancy, stem cells undergo differentiation. This is the process where stem cells migrate to different parts of the body and form specialized cells, such as muscle cells, nerve cells, or liver cells. During differentiation, stem cells can be affected by toxins. This can result in long-term effects, such as making the offspring susceptible to diseases later in life. Studies show prenatal and early-life exposure to arsenic may contribute to health issues that may show up during the offspring's adult life. This includes increased risk for metabolic diseases, such as high blood pressure and type 2 diabetes (T2D).

Water quality tests reveal that water sources in rural Western US states commonly contain arsenic. The Strong Heart Study (SHS), a longitudinal study of American Indian health issues, has shown that long-term exposure from various levels of arsenic is associated with metabolic conditions in American Indian communities, including T2D. Based on evidence from SHS data, scientists hypothesize children born in American Indian communities where arsenic is found in the drinking water have a higher risk of developing T2D and are more likely to be resistant to insulin.

The ***pancreas (PAN-cree-us)*** is an organ that produces the hormone ***insulin (IN-sull-en)***. Insulin is a complex molecular compound which helps turn food into energy. As we digest food, our body breaks down the food into smaller molecules, which include a simple sugar, known as ***glucose (GLUE-cose)***.



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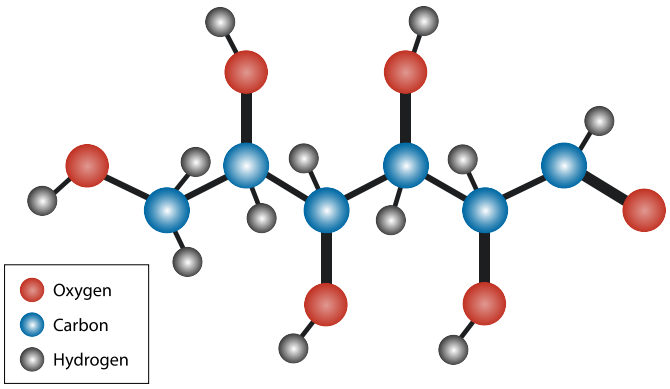
Glucose is made of carbon, oxygen, and hydrogen ($C_6H_{12}O_6$). Insulin bonds to glucose and "escorts" it into cells, where the cell ***metabolizes (meh-TAB-uh-lizes)*** the sugar. This means it breaks the chemical bonds of glucose which releases energy which is used by the cell. This energy enables us to move and supports body functions. However, sometimes the pancreas does not generate enough insulin. Without enough insulin, glucose levels in the blood are elevated. High levels of sugar in the blood can indicate insulin resistance or even T2D. With T2D, the amount of insulin produced by the pancreas cannot match the amount of sugar in the circulatory system. With insulin resistance, the pancreas needs to produce excess amounts of insulin to keep up with the glucose levels in the blood. With so much insulin floating in the circulatory system, the cells insulin receptors are overwhelmed. This means the amount of insulin in the blood exceeds the number of available insulin receptors. The cell may stop responding to the insulin. In other words, the cell becomes insulin resistant. When cells are insulin resistant, the cell does not respond to the insulin signal which tells the cell to take glucose out of blood circulation, causing the levels of sugar in the blood to drop. If the sugar cannot get into the cells, the level of sugar in the blood rises. Too much sugar in the blood from either T2D or insulin resistance can actually damage body tissues.

Glucose $C_6H_{12}O_6$



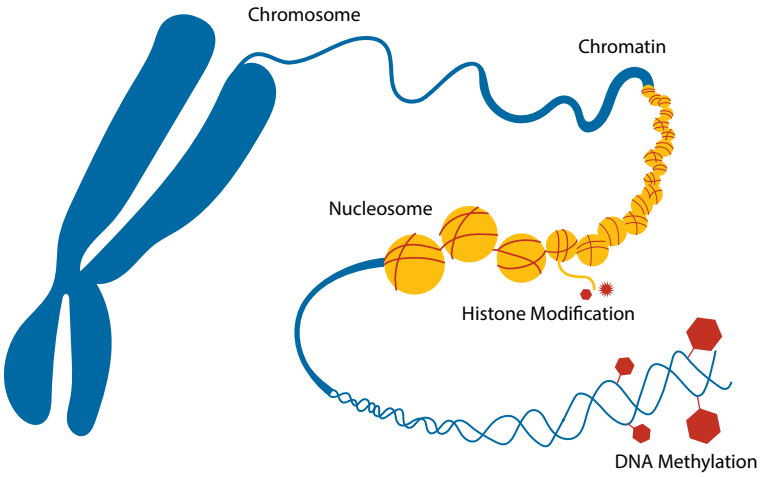
METHODS

The Strong Heart Study (SHS), is a cohort study in American Indian communities in the Southwest and Great Plains. Data from the SHS have led scientists to make a correlation between maternal exposure to arsenic during pregnancy and an associated increased risk of T2D or resistance to insulin, in their adult offspring. Thirteen American Indian communities participated in the SHS, including communities from North and South Dakota, Oklahoma, and Arizona. The SHS study included American Indian men and women, ages 45 - 74, from 1989 through 1991. The study participants were provided with an initial medical exam. Outcomes from the medical exams excluded some participants from the study cohort. Those who were able to participate were given annual follow-up exams for the duration of the study.

Collecting samples from participants required a 12-hour fast. Data obtained measured lipids, glucose, insulin and other metabolic markers. Fasting is important for getting accurate metabolic marker measurements because food intake can affect the levels of these markers in the blood. For example, eating a meal can raise blood sugar levels, which can make it difficult to get an accurate measure of insulin resistance. Insulin resistance is a major risk factor for type 2 diabetes.

The SHS provides a unique opportunity to identify potential epigenetic biosignatures of arsenic exposure on risk for T2D-related outcomes across generations. Biosignatures are molecules found in the blood that can provide evidence of exposure to arsenic, either early in life or present day. However, it is uncertain if these blood-based epigenetic signatures of exposure are related to offspring T2D-related ***phenotypes (FEE-no-types)***. Phenotypes are how the DNA is expressed as observable characteristics. The study set out to explore blood-based DNAm signatures of maternal arsenic exposure as a biomarker to assess T2D-related outcomes in adult offspring of mothers exposed to arsenic, during pregnancy and early life. A biomarker is a biological marker found in blood, body fluids, or tissues that is a sign of a normal or even abnormal process or condition or disease.

DNA methylation occurs when a small molecule called a methyl group (CH_3) attaches to a cytosine base on DNA strands. This epigenetic modification can be linked to prenatal and early life exposures to arsenic which can lead to future metabolic disease risk. Specific epigenetic information, including DNAm modifications, has been widely used as a potential biomarker of health and disease risk. To help identify those at a higher risk for metabolic disorders later in life, parental DNAm was collected from buccal cells (cells swabbed from inside the mouth), looking for biomarkers which could indicate metabolic diseases.



RESULTS

The SHS has collected a variety of data. For this study, characteristics of participants included gender, baseline body mass index (BMI) measurements, smoking status, median fasting glucose and waist circumference. Smoking status was categorized into the following three categories: Never smoked, Ever smoked and Current Smoker. See Table 1.

Table 1: Participant Baseline Characteristics

	SHS Mothers (n=119)	Offspring (n-226)
Age (years)	54.4 (49.3, 61.6)	40.4 (35.5, 47.2)
Sex (Male)	----	82 (36.2%)
Smoking Status	----	----
Never	44 (37.0%)	78 (34.4%)
Ever	32 (26.9%)	55 (24.3%)
Current	43 (36.1%)	93 (41.2%)
Waist Circumference (cm)	105.0 (98.0, 116.0)	100.0 (92.0, 111.0)
BMI (kg/m^2)	30.9 (27.2, 35.2)	30.4 (26.8, 34.9)
Diabetes Status (diabetic)	44 (37.0%)	0 (0.0%)
Follow-up Diabetes Status	41 (41.2%)	41 (18.1%)
Fasting Glucose (mg/dL)	111.0 (99.0, 168.0)	94.0 (87.0, 103.0)
Follow-Up Fasting Glucose (mg/dL)	113.0 (98.0, 171.0)	94.0 (86.0, 106.3)
HOMA2-IR (optimal score 1.4)	3.7 (2.4, 5.5)	1.5 (1.0, 2.5)
Follow-up HOMA2-IR (optimal score 1.4)	3.5 (1.9, 6.0)	1.6 (0.9, 2.7)
Total Arsenic (µg/g creatinine)	7.3 (5.0, 13.8)	4.6 (3.0, 8.4)

Discussion

The study found that DNAm signatures in the maternal lineage were associated with long-term metabolic health risk in offspring. This suggests that DNAm signatures in the maternal lineage may be a useful tool for assessing the risk of metabolic diseases in offspring.

DNAm may also influence offspring adiposity (body fat) and other offspring metabolic factors. This suggests that DNA methylation may play a role in the development of metabolic diseases such as obesity, type 2 diabetes, and heart disease. Mothers who were exposed to arsenic during pregnancy or early childhood may be at an increased risk of having children who develop metabolic diseases later in life.