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# Arsenic in Drinking Water: Affect the Gene Expression Related to type II Diabetes

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## ABSTRACT

Chronic exposure to high concentrations of arsenic in drinking water is associated with an increased risk for developing type II diabetes. The present revision focusses on the association of arsenic in water more than above normal, which might be affecting on the expression of genes related to type II diabetes with *in vivo* experimental evidence. We identified a few *in vivo* studies reported that arsenic interfered with transcription factors involved in insulin-related gene expression in pancreatic beta-cells arsenic decrease insulin synthesis, secretion and reduce the expression of antioxidant enzymes and in the liver whereas arsenic disturbs glucose productions by alteration of gluconeogenesis and abnormal proliferation. Currently available *in vivo* experimental study evidence shows that, the association between high and chronic exposure to arsenic in drinking water developing type II diabetes. But the effect of exposure to low or moderate levels of arsenic on risk in diabetes is unclear. An increase in the prevalence of diabetes mellitus has been observed among residents of highly arsenic contaminated areas.

**KEYWORDS:** Arsenic, Drinking water, Type II diabetes, Gene expression, Pancreatic beta-cells, Gluconeogenesis.

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## 1. INTRODUCTION

Type 2 diabetes mellitus is a metabolic disorder characterized by hyperglycaemias, insulin resistance in peripheral tissues, and altered insulin secretary capacity of pancreatic β-cells. Type 2 diabetes accounts for 90-95% of all cases of diabetes and is a major public health problem worldwide[1]. Established risks factors of type 2 diabetes include older age, obesity, physical inactivity, family history, and genetic polymorphisms.

In addition, environmental toxicants, including arsenic, have been suggested to play an etiologic role in diabetes development [2]. Arsenic is a recognized toxicant and carcinogen. Non-occupational exposure occurs mainly through drinking water, affecting millions of people worldwide. Exposure to levels of arsenic in drinking water well above 100 ppb has been associated with an increased risk of type 2 diabetes. Our objective was to perform a systematic review of the experimental studies (in vitro or in vivo) to synthesize available information on plausible mechanisms for gene expression which is related to type 2 diabetes.

The potential mechanisms proposed for arsenic-induced type 2 diabetes include, phosphorus substitution, high affinity for sulfhydryl groups, increased oxidative stress and interference with gene expression [3]. Arsenic has been shown to alter the expression of genes related to the maintenance of glucose homeostasis in tissues associated with the pathogenesis of the disease. Thus, arsenic could lead to diabetes by impairing the expression of a wide range of genes involved in pathways that maintain this homeostasis.

Pancreatic islets, adipose tissue, muscle and the liver, regulate glucose blood levels. Pancreatic β-cells secrete insulin in response to an increase in blood glucose levels. This hormone promotes the entrance of glucose into adipocytes and muscle cells via the glucose transporter GLUT4, and inhibits hepatic glucose production. The liver is responsible for gluconeogenesis, which maintains acceptable blood glucose levels when dietary glucose intake is insufficient. In addition, insulin stimulates cell growth and differentiation and promotes the storage of substrates in fat, liver and muscle by stimulating lipogenesis, glycogen and protein synthesis, and by inhibiting lipolysis, glycogenolysis and protein breakdown [4]. In the present review, we discuss the expression of genes involved in type 2 diabetes that are known to be affected by arsenic, identifying possible mechanisms or pathways by which arsenic could lead to or promote diabetes.

## 2. DEOXYRIBONUCLEIC ACID (DNA) METHYLATION

DNA methylation, a major regulator of epigenetic modifications has been shown to alter the expression of genes that are involved in aspects of glucose metabolism such as glucose intolerance, insulin resistance, β -cell dysfunction and other conditions, and it ultimately leads to the pathogenesis of type 2 diabetes mellitus (T2DM). Current evidences indicate an association of DNA methylation with T2DM. This review provides an overview of how various factors play crucial roles in T2DM pathogenesis and how DNA methylation interacts with these factors. Additionally, an update on current techniques of DNA methylation analysis with their pros and cons is provided as a basis for the adoption of suitable techniques in future DNA methylation research towards better management of T2DM. To elucidate the mechanistic relationship between vital environmental factors and the development of T2DM, a better understanding of the changes in gene expression associated with DNA methylation at the molecular level is still needed. [5-10]

Arsenic influences the sensitivity of insulin by changing the expression pattern of the genes involved in the insulin resistance and shifts away the cells from differentiation to proliferation status [11]. Many studies have shown the role of oxidative
stress and inflammatory response as the potent key mediator of arsenic induced toxicity [12-17]. Exposure to a low level of arsenite changes the gene expression of inflammatory cytokines such as interleukin 6 as well as genes involved in oxidative stress response leading to a decrease in insulin secretion, pancreatic islets dysfunction and changes in gluconeogenesis [18-23].The most extensively studied epigenetic mechanisms are the alteration of DNA methylation pattern and histone post-translation modifications, which in turn regulate the expression of genes at the level of transcriptional. Epigenetic changes such as DNA methylation alterations have been considered as a potential underlying mechanism in the pathophysiology of many diseases including Diabetes Miletus [24-27]. In DNA methylation critical genes which are involved in pancreatic development, insulin secretion and glucose sensing including insulin 2 (Ins2), pancreatic and duodenal homeobox 1 (Pdx1), peroxisome proliferator-activated receptor gamma (PPARγ) and glucose transporter 2 (Glut2), in order to evaluate DNA methylation alterations as a potent underlying mechanism of arsenic induced pancreatic dysfunction and diabetes development.[28-30]

### *2.1 Deoxyribonucleic Acid (DNA) Methylation Analysis*

Fazlullah khan[24] evaluated for the methylation status of the Pdx1, PPARγ, Ins2 and Glut2 genes after 6 days of exposure. The genomic DNA was isolated from 250 islets cells and was assessed for the amount, purity and integrity of DNA using ultraviolet–visible (UV) spectrophotometer and gel

electrophoresis. The bisulfite conversion procedures were performed as per the EZ DNA Methylation kit (Zymo Research Corporation, USA).Two separate bisulfite conversion treatment were performed for each DNA sample.

## 3. Messenger Ribonucleic Acid (mRNA)

Arsenic-induced alteration in mRNA insulin expression and secretion (pancreatic β-cell dysfunction) fits the model where insulin resistance alone is not enough to develop type 2 diabetes. Instead, both insulin resistance and insulin deficiency are needed in conjunction.

The mRNAs that were found significantly reduced were: (a) the transcription factor required for adipogenesis, peroxisome proliferative-activated receptor gamma (PPARγ); (b) the adipocyte selective fatty acid-binding protein (AP2) (induced by PPARγ); (c) the transcription factor CCAAT-enhancer binding protein alpha (C/EBPα) that works in conjunction with PPARγ to induce the expression of most fat cell-specific genes; and (d) genes involved in cell cycle regulation, like p21Cip1/Waf1 and p27Kip1[31,32].Arsenic exposure causes significant downregulation of mRNA expression of immune response related genes in most of the experimental groups[33,34] (Table 1)

**Table 1: Messenger Ribonucleic acid (mRNA) expression of immune response related to genes**

<table>
<tr><th>Sl No</th><th></th><th>Time</th><th>Temperature</th><th>Dose</th><th colspan="3">Effect</th></tr>
<tr><td rowspan="3">01</td><td rowspan="3">Dose dependent response [single exposure]</td><td rowspan="3">24h</td><td rowspan="5">-80°C</td><td>LD24</td><td colspan="3">Downregulated NFkb signalling genes</td></tr>
<tr><td>MD24</td><td colspan="3">Downregulated expression of inhibitor Nfkbia</td></tr>
<tr><td>HD24</td><td colspan="3"></td></tr>
<tr><td rowspan="2">02</td><td rowspan="2">Time dependent response [24h vs 48h]</td><td rowspan="2">24h vs 48h</td><td>LD24</td><td>6↓↑</td><td>5↑↑</td><td>One is unique to LD24</td></tr>
<tr><td>LD48</td><td colspan="3"></td></tr>
<tr><td rowspan="2">03</td><td rowspan="2">Effects of dose frequency</td><td rowspan="2">24h</td><td>RD</td><td colspan="3" rowspan="2">Expression of Chuk was downregulated</td></tr>
<tr><td>RDCE</td></tr>
</table>

LD24 - Low dose

MD24 - Medium dose

HD24 - High dose

RD - Repeated dose

RDCE-Repeated dose cessation

↓↑- Upregulated or Downregulated

↑↑- Upregulated

## 4. CONCLUSION

Millions of people all over the world are constantly exposed to iAs through the consumption of contaminated drinking water. Different mechanisms have been suggested for arsenic-induced diabetes. Our results showed that arsenic exposure alters DNA methylation status of key insulin-related genes. Also, we found that sodium arsenite impacts the expression of other key regulatory genes involved in insulin metabolism and therefore could result in the impairment of islets function. There is a possibility of the involvement of other epigenetic regulatory mechanisms such as histone post-translational modifications or microRNA dysregulation that remained to be explored in the future. Additionally, a further longitudinal in vivo study is suggested to establish the sodium arsenite-induced methylation changes as the underlying mechanism involved in islet dysfunction. Our results reinforce the importance of future research on arsenic-induced epigenetic modifications aiming at finding therapeutic or prognostic factors.

This study demonstrated that exposure to arsenic may have substantial effects on gastrointestinal health, possibly through the gene expression of the various immune response-related pathways. While the potential health effects of long-term arsenic exposure are well known, it is important to address the lack of knowledge of the impact of low doses of arsenic on gastrointestinal health. These data show that low-level arsenic exposure may have a dramatic impact on immune system preparedness, even after a single exposure.

The effects of arsenic both altering pancreatic ß-cell function and glucose uptake in peripheral tissues, which resemble type 2 diabetes, suggest that these mechanisms play an important role in the increased incidence of type 2 diabetes in chronically exposed to chronic inorganic arsenic(iAs)

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