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A Critical Correlation between Arsenic Toxicity and Risk of Type 2 Diabetes

Kainat Aftab, Huda Rehman Mir*, Manam Walait and Mahida Mehmood

Department of Biotechnology, University of Central Punjab, Lahore, Punjab, Pakistan

**Corresponding e-mail: hudamir22@gmail.com*

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ABSTRACT

Arsenic is considered one of the most lethal elements to humans because of its adverse health effects. Worldwide arsenic is contaminating groundwater and it has been reported in different areas of the world that drinking water carries Arsenic into the human body. That has helped researchers develop a link between exposure to Arsenic due to drinking water and the prevalence of diabetes. When Arsenic enters the body, the human gene AS3MT plays a pivotal role in its methylation and metabolism. The intronic and exonic single nucleotide polymorphisms in the AS3MT gene show heterogeneity due to inter-individual variation. To note that type 2 diabetes is a disorder caused by insulin resistance, hyperglycemia and a change in insulin secretory capacity of pancreatic β cells. The exposure to chronic levels of Arsenic interferes with the transcriptional factors involved in linked gene expression. Previously epidemiological studies revealed the inconstant effects of arsenic on glucose metabolism but there is only limited data on arsenic induced type 2 diabetes mellitus. The objective of this review article is to analyze the alarming rise of arsenic toxicity in drinking water around the globe and how it causes type 2 diabetes. While understanding the association of AS3MT gene polymorphism and arsenic metabolism to understand the intensity of the causes and effects of Arsenic exposure.

Keywords: Arsenic, AS3MT, Arsenic methylation, Type 2 diabetes, Arsenic methylation, Single nucleotide polymorphism

INTRODUCTION

Heavy metal toxicity is linked with an increased risk of spreading chronic diseases in the human body [1]. Exposure of different chemicals in drinking water has now turned out to be a major environmental issue worldwide and among these toxic chemical's arsenic is the best characterized. Arsenic is a naturally occurring environmental contaminant that is widely spread in Earth's crust, containing about 3.4 ppm arsenic. It is considered one of the most dangerous elements to mankind because of its outspread range of health issues and immense distribution in the environment. Exposure to inorganic arsenic is the main cause of the majority of arsenic induced health issues, with inorganic arsenic round about one hundred million individuals are at risk from natural contamination of aquifers [2]. Different diseases including respiratory conditions, change in skin pigmentation, several types of cancer and diabetes are associated with exposure to uplifted concentrations of inorganic arsenic.

Arsenic contamination in drinking water

In drinking water, current proposed limit of arsenic according to WHO guideline is 10 µg/L; although this value is designated as temporary because of the problems in removing arsenic from drinking water therefore concentrations

should be kept as low as possible. A number of people are exposed to arsenic at concentrations more than the normal guideline value set by WHO and this cause serious health issues both at individual and [3] population level. Arsenic is classified as a group 1 carcinogen by International Agency of Research on Cancer (IARC). Since 2010, ground water contamination caused by arsenic has been WHO's major public health concern.

In different countries arsenic poisoning from drinking groundwater is an upshot of either natural or anthropogenic sources and a number of people from different ethnicities are heavily dependent on groundwater that contain an immense amount of Arsenic (As) for drinking purpose. There are different sources through which Arsenic (As) can enter human body including drinking water, inhalation, eating food and via some anthropogenic sources that may include wood preservatives and commercially used pesticides but above all the primary source of human exposure to As is contaminated groundwater water [4].

Organic arsenic toxicity is normally less than that of inorganic arsenic and arsenic found in drinking water is normally in the form of inorganic arsenate or arsenite that is not good for human health. Inorganic arsenic exposure primarily through drinking contaminated water for a long time period can lead to chronic arsenic poisoning; therefore detoxification of arsenic is necessary. Heavy metal detoxification is a process in which metallic toxic substances are removed from the body and for the biotransformation of As methylation is a vital metabolic pathway [5]. Methylation of arsenic is basically a process of detoxification through speed up excretion.

LITERATURE REVIEW

This review aims to highlight the association of different intronic and exonic AS3MT SNPs, arsenic metabolism and risk of type 2 diabetes in people exposed to Arsenic contaminated drinking water. The harmful effect of Arsenic toxicity and its detrimental effects on human health have been reviewed in this article [6]

Arsenic biotransformation

It includes two main steps methylation and reduction. Before arsenic can be further metabolized, pentavalent arsenate is reduced to trivalent arsenite mainly in the blood that is taken up in the liver. In human, methylation of inorganic arsenic is considered as a detoxification mechanism because methylated Mono-Methylarsonic acid (MMA) and Di-Methylated Arsenic (DMA) are rapidly excreted through urine. An average amount of arsenate is reduced to arsenite through Glutathione (GSH) and the methylation process takes place in cytosol catalyzed by methyl group transfer through S-adenosylmethionine. For the methylation of arsenic [7], liver is considered the major site because of its mass and ingested arsenic can pass through it easily.

Previously methylated and di-methylated arsenic were considered less toxic but now according to recent studies trivalent intermediates, Mono-Methylarsinous acid (MMA^{III}) and Di-Methylarsinous acid (DMA^{III}) are considered more toxic [8]. The ability to metabolize inorganic arsenic varies among individuals. In order to achieve a more precise estimation of arsenic methylation capacity, it is mandatory to find out the particular arsenic species derived from inorganic species that are eliminated through urine, as an average amount of arsenic intake is excreted in the urine and the main urinary metabolite that is eliminated in human urine is DMA (V).

Trivalent arsenic species, As (III) are more powerful protein binders as compared to pentavalent arsenic species. In methylation process ionizable hydroxyl group is replaced by uncharged methyl group that leads to the formation of less negatively charged arsenic species, that have the ability to interact directly with negatively charged molecules like DNA, because of these biochemical properties trivalent arsenic species are considered more toxic then trivalent arsenite species. TMA^{III} could be poisonous because they do not contain ionizable hydroxyl groups that can limit their binding with DNA [9]. For the metabolism of inorganic arsenic corresponding levels of urinary arsenic can be used as an indicator. The uncharged ratio of ingested dosage of arsenic depends on the amount of inorganic arsenic present in urine and the amount of MMAV and DMAV respectively shows the first and second methylation phase. Organic arsenic is also found in the urine but it is nontoxic. Urinary total arsenic is represented by MMAV and DMAV. Observation that human beings eliminate more MMAV in urine than other species tells us the importance of complete second methylation.

In humans arsenic methylation is catalyzed by a key enzyme Arsenic (+3 oxidation state) Methyltransferase (AS3MT). AS3MT gene also known as CYT19 is round about 32 kb long, consists of 11 exons and located in chromosome band 10q24. AS3MT catalyzes the methylation of arsenic first to MMA then to DMA and this is the only reported function. Importance of AS3MT gene in the methylation process of arsenic has already been shown in

many *in vitro* studies. The normal figure of urinary arsenic consists of 10 to 20% monomethylated arsenic and 60 to 80% dimethylated arsenic and a variation in this normal urinary figure can bring genetic polymorphism in the gene related to arsenic metabolism [10].

AS3MT SNPs and their effect on gene function

Some SNPs have no significant effect on the functioning of genome but can bring slightest change in the expression of genes and play an important role in our body, they occur in the noncoding region of the genes and gene related sequences, just like in AS3MT gene different intronic SNPs have been linked with the variation in arsenic metabolite pattern, despite being noncoding these SNPs can change the expression of a gene. According to previous studies intronic SNPs that were shown to be related to inter-individual change includes G7395A, G12390C, T14215C, T35587 and G35991A. On the other hand, there are also some nonsynonymous SNPs, including missense and nonsense that can make the protein nonfunctional, they have also been linked with the change in arsenic metabolite pattern and are known as exonic SNPs [11]. Three exonic SNPs in AS3MT gene have been identified M287T, R173W and T306I. Among these exonic SNPs that were found in the exon of AS3MT, M287T is best characterized.

Arsenic induced type 2 diabetes

Arsenic is a toxicant and immense and overlong exposure of inorganic Arsenic (iAs) with drinking water has adversely affected human health causing different types of diseases including cancer, hypertension, anemia, peripheral vascular disease and diabetes. Increased level of arsenic above 100 ppb has increased the risk of type 2 diabetes in many parts of the world. Type 2 diabetes is a medical condition in which body can produce insulin but the body is unable to use it the way it should. It's the most common type of diabetes and also known as adult-onset diabetes. Insulin is a hormone produced by our pancreas that let the blood sugar into the cells of our body to be used as energy, but sometimes glucose builds up in your blood instead and cause problems in our body. People with type 2 diabetes are known to have insulin resistance, our pancreas makes more insulin in order to get cells to respond but they cannot keep up and eventually our blood sugar level rises. High blood sugar level is not good for the body and can lead to serious health problems. The main source of energy is blood glucose that we get from eating food [12]. This type of diabetes can develop at any age but most common in older people. Factors causing type 2 diabetes includes age, family history, overweight, obesity and ethnicity but sometimes symptoms of type 2 diabetes are not noticeable at all therefore by keeping in view the risk factors blood sugar test must be performed. Some environmental toxicants like arsenic also play a role in the development of diabetes.

It was initially reported that arsenic present in drinking water disturbs the insulin secretion in pancreas increasing the risk of diabetes. In many countries like Mexico, Bangladesh, Taiwan through different epidemiological studies it was observed that arsenic exposure was linked with an increased risk of type 2 diabetes. Increased prevalence of type 2 diabetes is observed in the areas that are highly arsenic contaminated. Disruption of insulin stimulated glucose uptake is the result of chronic arsenic exposure to develop type 2 diabetes in human [13]. In earlier studies and association of urinary percentage of $DMAs^{III}$, a toxic product of arsenic methylation by AS3MT and diabetes was reported.

There are also some other genes including GSTO and PNP that can have an impact on arsenic methylation and can cause different diseases. GSTO1, glutathione S transferase ω is an enzyme that plays a modest modification role in arsenic methylation as it is responsible for reduction of pentavalent species of arsenic. In the methylation process, GSTO is needed in a variety of animals including humans. Different studies revealed association between GSTO SNPs and cancer susceptibility. There are two members of GSTO named as GSTO1 and GSTO2. Until now three polymorphisms in hGSTO genes have identified including A140D, E155del and N142D. PNP, purine nucleoside phosphorylase is an enzyme that is involved in purine metabolism. One SNP rs1049564 has been identified in PNP that were linked with higher levels of IFN in SLE. Although studies performed in different countries are still insufficient to find out the impact of GSTO and PNP gene on arsenic metabolism so to find out their impact on methylation further studies are required [14].

The objective of the study is to observe the association between arsenic exposure and type 2 diabetes because data on the current topic, intronic and exonic SNPs and their prevalence in different ethnicities is insufficient.

As3MT gene polymorphism

Arsenic is one of the main causes of ground water contamination worldwide, methylation is important for the biotransformation of arsenic. Arsenic methylation is catalyzed by human AS3MT gene (hAS3MT), this gene produces intracellular metabolites that are considered more toxic then inorganic arsenic and causes arsenic induced health issues. Several inter-individual variations have been reported in arsenic metabolism. Different single nucleotide polymorphisms found in human AS3MT gene were shown to be protective but three exonic SNPs (R173W, M287T, T3061) that were previously identified can be deleterious. Intronic SNPs (H51R, C61W, I136T, W203C, R215H) were also identified in human AS3MT gene. Most of the SNPs are neutral and they may have a little or no effect on human health. However, it was reported that a exonic SNP M287T in human AS3MT gene has been linked increased risk of arsenic induced diseases such as cancer, skin lesions and diabetes.

Within AS3MT genes different genetic polymorphisms were identified in different populations including Japanese, Chinese, Tibetans, Mongolians, Tamils, Sinhalese in Asia, Ghanaians and Africans. To check the toxic effects of arsenic and variation in metabolism at individual or population level different studies in different population regarding genetic analysis of SNPs within in AS3MT gene were performed [15]. Different arsenic compounds present in the body are considered to have an association with the metabolic action of AS3MT. In some epidemiological studies it has been showed that individual who had higher percentage of DMA in urine could exude more arsenic from the body because of higher arsenic methylation ability while in other epidemiological studies higher concentrations of MMA in urine of individuals with arsenic induced diseases were reported. According to the previous studies certain enzymes like AS3MT that have the ability to metabolize arsenic through methylation could be one of the factors linked with variation of arsenic methylation. In humans AS3MT genetic polymorphism, most of the SNPs identified were conflicting however, two SNPs rs3740393 and rs11191439 were constantly related to arsenic methylation.

Epidemiological data on human AS3MT genetic polymorphism and arsenic metabolism in different populations

It is notable that individuals vary in the amount and distribution of arsenic metabolites that are eliminated in urine. In Taiwan different studies were performed to find out the genetic association between urinary arsenic figures and polymorphism of AS3MT, a key enzyme that catalyzes the methylation process of arsenic. To examine polymorphisms of AS3MT, 70 individuals were selected who were previously exposed to arsenic and the gene was re-sequenced. According to the results total 16 polymorphisms were identified including 11 SNPs that were located on introns and 3 insertion/deletion polymorphisms, an exonic SNP M287T and a VNTR found on exon 1 within an area of 5′ UTR.

In northwest China, individuals exposed to environment contaminated with arsenic were more likely to develop diseases related to arsenic metabolism. In Gansu Province the concentration of arsenic found in drinking water was 969 μg/L that was 100 times higher than the normal guideline value of arsenic recommended by WHO (10 μg/L). Different epidemiological studies were performed to examine the association between AS3MT SNPs and arsenic induced disease. 850 individuals were selected out of which 331 were patients who were suffering from the disease and 519 were control patients. According to the results 13 AS3MT SNPs located on intron on were identified and individuals with rs1078835 (A35991G) polymorphism who were carrying AG genotype were more susceptible to develop disease than individuals carrying AA genotype [16].

In different areas of Mexico different case studies on human population regarding AS3MT gene polymorphism were studied. In Yaqui Valley of Sonora, Mexico, the concentration of arsenic found in drinking water was 43.3 μg/L. By studies it was revealed 3 exonic SNPs (rs12767543, rs11191453 and rs3740393) were identified on AS3MT genes that were associated with urinary arsenic metabolism. In the urine of entire population, AS3MT SNPs were associated with DMA [V]/MMA [V]. According to analysis this association was found only in children and not in adults. Amount of DMA [V]/MMA [V] in urine of individuals with rs1267543 and rs3740393 polymorphism were lower as compared to rs11191453. Results revealed significant association of MMA (V) percentage with M287T.

In the population of Argentina significant association between arsenic metabolism and genetic polymorphisms in AS3MT was reported. In the northern Argentinean Andes, arsenic metabolites in the blood, urine and buccal cells along with variation in AS3MT of 147 indigenous women were found. Arsenic concentration found in drinking water was about 200 μg/L and individuals were exposed to this concentration. After studies 9 different SNPs were

examined in AS3MT, including rs3740393, rs17881367, rs11191439, rs10748835, rs7880342, rs17881367, rs17880342, rs3740400 and rs3740393. Among those identified SNPs two intronic SNPs rs10748835 and rass3740390 were found to have a significant relationship with secondary methylation step of arsenic metabolism. Lower percentage MMA (V) and higher percentage DMA (V) and DMA (V)/MMA (V) in the urine of individuals carrying AA allele of rs10748835 as compared to individuals carrying GG and GA allele.

In different populations of Europe including Hungary, Slovakia and Romania who had been exposed to low levels of arsenic, relationship between arsenic metabolism and genetic polymorphism in AS3MT was examined. This study was quite different from others as the individuals were exposed to lower arsenic concentration (8.0 µg/L) and number of arsenic metabolites varied widely in the urine. Through different studies it was revealed that one exonic SNP rs11191439; M287T was the major factor that may affect arsenic metabolism. Individuals with TC+CC allele had lower DMA (V) percentage and higher MMA (V) percentage than individuals with TT allele.

In African-American and Caucasian-American functional analysis of human AS3MT gene was performed. Sixty individuals were selected from Caucasian-American and sixty were selected from African-American. Total 26 SNPs and one VNTR were identified in the individuals and among those identified SNPs 3 exonic SNPs including M287T, A173T and T306I were non-synonymous. According to the results, immunoreactivity protein expression and enzyme activity of 287T variant was higher in individuals that were treated with 12.5 nM As (III) than those of the wild types, while 306I and 173T variants showed different results. The researchers concluded that genetic variation in AS3MT may contribute to individual differences in the function and expression of AS3MT (Table 1).

Table 1 Prevalence of arsenic induced type II diabetes in different ethnicities

Ethnicity	Source of Arsenic exposure	Population size (n)	Male/female%	Diabetes diagnostic test	Arsenic concentration	References
Bangladesh	Drinking water	300	26% male 74% female	Fasting blood glucose test	0.07 to 1.4 ppm	(Nehsa, Islam et al.)
Bangladesh	Drinking water	1004	68.4% female 31.6% female	Fasting blood glucose test	Over 50 µg/L	(Islam, Khan et al.)
Taiwan	Drinking water	660	Random ratio	Oral glucose tolerance test	Less than 2 µg/L	(Navas-Acien, Silbergeld et al.)
Cambodia	Drinking water	142	43 male 99 female	Fingertip blood glucose test	907.25 µg/L	(Huang, Cheng et al.)
Mexico	Drinking water	258	65 male 109 female	FBG test OGTT test FPI HbA1c	3 to 215 ppb	(Del Razo, García-Vargas et al.)
Thailand	Drinking water	385	50 % male 50% female	HbA1c	0.1 to 68.63 µg/g	(Sripaoraya, Siriwong et al.)
Chile	Drinking water	2203	1242 male 961 male	FBG	83.1 ng/L	(Sung, Huang et al.)
US Adults	Drinking water	788 adults	Odd ratio	Fasting serum glucose	7.1 µg/L	(Navas-Acien, Silbergeld et al.)
Serbia	Drinking water	383	Odd ratio	Oral glucose tolerant test	1.0 to 349.0 µg/L	(Jovanovic, Rasic-

						Milutinovic et al.)

Studies on HAS3MT allele frequency in different populations

Worldwide in different countries different studies were performed on different SNPs found in AS3MT that were influencing arsenic metabolism. Although, the information available on frequencies of genetic variation in AS3MT gene for number of SNPs and relationship with ethnicity is limited. Since 2007 arrangement of SNPs in some Asian populations including Japanese, Chinese, Tibetans, Ghanaians, Vietnamese and Mongolians were reported. According to the results of epidemiological data some allele frequencies followed Hardy-Weinberg equation and some allele frequencies didn't follow Hardy-Weinberg equation may be because of small sample size and because no genotype error was observed in duplicate investigation. Allele frequencies of SNPs in different population were compared with the recent studies and according to the results notable variations among the populations (Table 2) were found for other SNPs. For ASTMT rs7098825 polymorphism C alleles were low in the populations including OVA, SLT, GH, YRI, MN and SLS. For AS3MT rs12767543 polymorphism, NP has no C allele. An allele of rs72920657 and rs12767543 were found in CH, VN accordingly and C allele frequencies of rs17879819 were higher in populations of GH and OVA as compared to Asians. More research work is required to understand the variations in AS3MT gene (Table 3).

Table 2 AS3MT intronic SNPS reported in different populations

Intronic SNPs reported	**SNP ID**	**Populations**	**Sample used**	**References**
G12390C T14215C A355991G	rs3740393 rs3740390 rs10748835	Mexicans	Buccal cells and urine sample	(Gomez-Rubio, Meza-Montenegro et al.)
T35587C G7395A G12390C	rs11914653 rs12767543 rs3740393	Vietnamese	Human hair, urine and blood	(Agusa, Iwata et al.)
A35991G	rs10748835	Rural Texas	Blood samples	(Edwards, Hall et al.)
T14215C G12390C T35587C G35991A G7395A	rs3740390 rs3740393 rs11914653 rs10748835 rs12767543	Mongolian Korean Japanese	Blood or blood strain	(Fujihara, Fujii et al.)
A5194C G12390C A35991G C14215T T12590C	rs3740400 rs3740393 rs10748835 rs3740390 rs3740390	Argentina	Urine, buccal cells and blood	(Schläwicke Engström, Broberg et al. 2007)
G12390C	rs3740393	Taiwan	Urine	(Agusa, Fujihara et al.)
T14215C G12390C	rs3740390 rs3740393	Turkish Ovambo	Blood samples were collected	(Gomez-Rubio, Meza-Montenegro et al.)

T35587C G35991A G7395A	rs11914653 rs10748835 rs12767543			
A4602G A7395G C25986T C35587T A27215G	rs7085104 rs12767543 rs7085854 rs11191453 rs11191446	Chinese Tibetans Nepalese	Blood samples, urine	(Gomez-Rubio, Meza-Montenegro et al.)
A6144T A35991G A8979T A10209G	rs17878846 rs10748835 rs7920657 rs3740394	Srilanka-Tamils Srilanka-Sinahalese Ghananians	Blood and urine samples	(Agusa, Fujihara et al.)

Table 3 AS3MT exonic SNPs reported in different populations

Exonic SNPs	**SNP ID**	**Populations**	**Sample used**	**References**
M287T	rs11191439	Mexico	Fasting blood	(Drobná, Del Razo et al.)
R173W M287T T306I	rs17881215 rs11191439 rs34556438	Vietnam	Urine, human hair and blood	(Agusa, Iwata et al.)
M287T R173W T306I	rs11191439 rs17881215 rs34556438	African Americans and Caucasian Americans	Urine	(Li, Packianathan et al.)
M287T	rs11191439	Chile	Urine	(Agusa, Fujihara et al.)
M287T	rs11191439	India	Nails and hair sample	(Agusa, Fujihara et al.)
M287T	rs11191439	Iranian	Genomic DNA extracted from blood	(Farhid, Nadali et al.)
M287T	rs11191439	Japanese Korean Tamils Ovambo Ghanaians	Blood or blood strain samples	(Fujihara, Soejima et al.)
M287T	rs11191439	Turks Xhosas Tibetans Central European Sinhalese	Genomic DNA extracted from blood	(Hernández, Xamena et al.)

		Uygurs		

Human As3MT VNTR

VNTR are basically variable number of tandem repeats. Epidemiological studies performed in two different populations Caucasian American and African Americans revealed the presence of VNTR in human AS3MT gene (Table 4). Sixty DNA samples from Caucasian Americans and sixty from African Americans were collected and according to the results within an area encoding cDNA 5-untranslated region, variable number of tandem repeats in EXON 1 were observed.

Table 4 VNTR in EXON 1

Location	Nucleotide change	Variant Allele frequency in Caucasian Americans	Variant allele frequency in African Americans
5′ FR	G/A	0.000	0.025
5′ FR	T/C	0.017	0.000
5′ FR	A/G	0.383	0.317
5′ FR	G/C	0.117	0.242
5′ FR	C/A	0.000	0.008

DISCUSSION

Pathophysiology of diabetes mellitus: DM is a metabolic disorder due to which high blood sugar is caused. Insulin is a hormone released from pancreas that helps glucose to move from blood into cells to be used immediately or stored for energy. Throughout the day blood glucose level vary in the blood normally, but after taking a meal it raises. In healthy people a narrow range of blood glucose level is about 70 to 110 mg/dL but aged people may have higher levels. A diabetic patient is unable to produce enough insulin to move sugar from blood into cells or to use insulin effectively. There are two types of diabetes and different factors are linked with each type [17].

Type 1 diabetes: Commonly known as insulin dependent diabetes. In this type of diabetes, the immune system of body attacks insulin producing pancreatic β cells and destroy them permanently due to which pancreas produce little or no insulin. Different environmental factors are associated with type 1 diabetes like a nutritional factor or viral infection. This type is not very common in people only a few percentages of individuals with diabetes have type 1 diabetes.

Type 2 diabetes: Commonly called non-insulin dependent diabetes. In this type of diabetes pancreas produce insulin above the normal level due to which body develops resistance against the effects of insulin and a very low amount of insulin is left to meet the body's need. T2DM is characterized by hyperglycemia, microvascular and macrovascular complications. Different environmental factors and genetic factors including obesity, physical inactivity is associated with type 2 diabetes. Impaired insulin secretion and insulin resistance are the key defects in T2DM, but some other pathophysiological abnormalities are also involved that cause the dysregulation of glucose metabolism. There are multiple factors that are the cause of failure of pancreatic β cells including glucotoxicity, ageing, incretin hormone (GLP1) resistance and hypersecretion of IAPP and activation of inflammatory pathways. For the diagnosis of T2DM different tests can be performed like blood glucose measurement, hemoglobin A1C and oral glucose tolerance test.

Correlation of arsenic toxicity with risk of diabetes mellitus: Previously it was reported that arsenic exposure in the environment contributes to diabetes development. Different *in vitro* studies were performed to observe the association between arsenic and glucose metabolism out of which five studies showed that arsenic intervenes with the transcription factors that are involved in insulin linked gene expressions including peroxisome proliferative

activated receptor γ and upstream factor 1. Some other *in vitro* studies reported that the effect of arsenic on glucose uptake is mainly due to increased amount of arsenate or arsenite in the body.

An increased prevalence of diabetes mellitus has been investigated among individuals living in the areas that were highly contaminated with arsenic. Although arsenic induced diabetogenic effect are still upon debate, current *in vitro* studies showed that inorganic arsenic, arsenate or arsenite impair glucose stimulated insulin secretion. Various cross-sectional studies from Taiwan and Bangladesh indicated a link between chronic consumption of drinking water that contains an elevated amount of inorganic arsenic and prevalence of diabetes.

In vitro **experimental studies:** Pancreatic islet β cells release a metabolic hormone called insulin that activates principal responses to lower blood sugar level by stimulating glucose uptake in the peripheral adipose tissue and skeletal muscles. Insulin in the liver also suppresses the glycogenolysis and gluconeogenesis. Insufficient amount of insulin in the body causes deleterious effects on glucose homeostasis and glucose transport in the pancreatic β cells may influence insulin resistance. When glucose enters into the cell through a transporter leading to the production of adenosine triphosphate it closes the adenosine triphosphate-sensitive potassium channel and opens up the voltage dependent calcium channel found in the cell membrane, single transduction pathway begins.

Under diabetic condition oxidative stress is induced that is involved in dysfunctioning of pancreatic β cells. Because of low levels of antioxidant enzymes, pancreatic β cells are vulnerable to the damage caused by oxidative stress. Although mechanism due to which arsenic induce diabetes is still not defined but current *in vitro* studies showed that iAs impair insulin-dependent sugar uptake. Different studies reported that low level arsenite round about 0.5 to 2 μM; trivalent arsenic species and oxidative stress in pancreatic β cells impair insulin secretion. These experimental studies suggested that arsenic has an association with diabetes by impairing functions of pancreatic β cells specifically insulin secretion and synthesis.

Cross sectional studies on arsenic induced type 2 diabetes in different ethnicities: Current studies indicated that trivalent species of inorganic arsenic plays a vital role in the development of diabetes. In different areas of Mexico where drinking water was highly contaminated with arsenic, several studies were conducted to observe the association between arsenic exposure in drinking water and prevalence of diabetes. A total of 258 individuals were selected including males, females and children and their urine and blood sample was collected for diagnostic test. The amount of inorganic arsenic in the drinking water samples collected from different regions of Mexico was about 3 to 215 ppb and the amount of trivalent arsenic in the urine sample was about 2 to 234 ng As/Ml. Results characterized by fasting hyperglycemia revealed that arsenic was associated with diabetes.

Arsenic presence in drinking water is a serious public health issue in Serbia. To observe the association between arsenic and diabetes type 2 a cross sectional study in two different populations of Serbia was performed. One was exposed population inn middle Banat region where the amount of arsenic in drinking water was 56 μg/L and other was unexposed population from six areas in Central Serbia where the amount of arsenic in drinking water was 2 μg/L. Both the population were compared by family history of diabetes, age and prevalence obesity and the results of the cross sectional study performed indicated that population from middle Banat region exposed to low level of arsenic were at higher risk of developing diabetes type 2.

It has been reported in Bangladesh that arsenic exposure can be a potential risk factor for the development of diabetes type 2. A cross section study was performed among the individuals of Bangladesh to find out the association between arsenic exposure and prevalence of diabetes type 2. A total of 1004 individuals were selected for the experimental studies. The amount of arsenic in the drinking water samples was above 50 μg/L. A diagnostic test, using glucometer was performed for T2D cases and the family history, BMI information was collected to observe the association. Results revealed that individuals who were exposed to arsenic level above 50 μg/L were at higher risk of developing diabetes type 2 and the prevalence of diabetes 2 among the residents of Bangladesh was 9% [19].

A cross sectional study was conducted in Cambodia to find out the association between arsenic and type 2 diabetes. Residents of Cambodia had a Non Western style diet and the amount arsenic found in the drinking water was 972 μg/L. A total of 142 individuals were selected including odd ratio of males and females and according to investigation 14 were found to have DM. Urine samples, blood samples and water samples were collected and different diagnostic tests were performed. Results showed that arsenic amount above 907.25 μg/L were associated with increased risk of developing diabetes mellitus.

Genetics of arsenic methylation: Not only AS3MT but there are also some other genes that have an impact on arsenic methylation including N6AMT1, GSTO and PNP. Polymorphism in these genes can bring changes in arsenic methylation that will ultimately cause susceptible diseases.

N6AMT1: Recently it was reported that N-6 adenine specific DNA methyltransferase 1 has the ability to convert highly toxic monomethylarsonous acid to less toxic dimethylated arsenic. Based on experimental studies and different observations it was revealed that N6AMT1 can change arsenic metabolic profile and have the ability to change genetic susceptibility of humans and can increases arsenic induced health diseases. A study was conducted in the population of inner Mongol, China. 289 individuals were selected to find out the association between urinary arsenic profiles N6AMT1. According to the results, five different N6AMT1 SNPs were identified including rs7282257, rs2248501, rs1003671, rs2738966 and rs2065266. Amount of arsenic in drinking water of Inner Mongolia was higher than 10 µg/l. Blood and urine samples were collected, DNA extraction and PCR sequencing was performed to find out the association.

GSTO: There are two members of glutathione S-transferase omega, GSTO1 and GSTO2 that are involved in the metabolization of xenobiotics such as arsenic. GSTO is an enzyme that is responsible for the reduction of sMMAV and DMAV and also catalyzes the reduction of DMAV to DMAIII and AsV to AsIII. Experimental studies were performed to find out either SNPs in GSTO were associated with urinary arsenic profile or not and for these purpose different individuals susceptible to arsenic induced skin lesions were selected from different regions of Bangladesh. Water and urine samples of the participants were collected, DNA extraction and PCR sequencing was performed. One GSTO1 SNP Ala140Asp and two GSTO2 SNPs, Asn142Aso and rs2297235 were identified after sequencing. Results revealed that GSTO2 SNP rs229735 had higher urinary arsenic concentrations although role of GSTO1 was not fully understood [20].

PNP: PNP gene is involved in purine metabolism and it was reported that PNP gene has an association with arsenic metabolism although the data is insufficient on PNP SNPs to find out their impact on arsenic metabolism.

CONCLUSION

Overall, information from human studies included in this critical review article supports an association between arsenic exposure through drinking water and type 2 diabetes, but current available data is still not enough to conclude that arsenic is linked with diabetes. Flaws noted in literature review included insufficiency of arsenic exposure measurement methods, self-reported diagnosis for identification of type 2 diabetes and prospective studies. Because of these few limitations, the evidence of correlation between arsenic exposure and diabetes ranged from limited to sufficient. Stronger evidence of correlation with good measures of outcome and exposure requires further research in different ethnicities. There are some research needs that must be fulfilled including impact of BMI, physical activity, impact of arsenic metabolism, potential risk of type 2 diabetes, exposure data on arsenicals and Cross-sectional studies with reported cases of type 2 diabetes to evaluate the association. In countries like Mexico, Bangladesh, Taiwan, India, Pakistan where type 2 diabetes is epidemic, the above mentioned research needs should be better addressed. In addition, further studies must include environmental interactions and studies of AS3MT polymorphisms that are linked to arsenic metabolism and type 2 diabetes sussceptibility.

- Diabetes prevalence due to arsenic exposure is reaching epidemic proportions in different countries of the world.
- Epidemiological data on association between arsenic exposure and diabetes type 2 through groundwater is limited.
- Future studies must include environmental interactions, including studies of AS3MT SNPs.
- More *in vitro* experimental studies should be performed in research laboratories to observe the association between arsenic exposure and type 2 diabetes.

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