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RESEARCH ARTICLE

Association of Chronic Arsenic Exposure with Insulin resistance in Gestational Diabetes Mellitus

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Abstract

Background and Aims: Chronic exposure to arsenic is associated with a number of adverse health effects. Association of chronic arsenic exposure with diabetes mellitus is fairly well established, but the association of arsenic toxicity with glucose intolerance and insulin resistance in pregnancy have yet not been studied adequately. The present study was undertaken to explore the association of chronic arsenic exposure with insulin resistance in gestational diabetes mellitus (GDM).

Methods: Under an observational cross-sectional design a total of 79 pregnant mother (age in yrs, M±SD, 23.05±4.47) residing in an arsenic affected area of Bangladesh were included in the study. GDM was diagnosed by DIPSI criteria (2013). Clinical and anthropometric measurements were done by standard techniques. Arsenic exposure was assessed by the level of as in the usable tube-well (Green, Red Identified) water at the respective households. Participants had urinary arsenic level higher than 100 µg/L was categorized as arsenic exposed and lower than 100 µg/L were categorized as non-exposed. Serum glucose was measured by Glucose Oxidase method, serum insulin was measured by ELISA method, Insulin Sensitivity (HOMA%S) and Insulin resistance (HOMA% IR), were measured by Homeostatic Model Assessment and as level in urine and Serum was measured by ultraviolet/visible spectrophotometry.

Results: Out of the 79 pregnant mothers 38 GDM and 41 non-GDM mother enrolled in this study. Urinary Arsenic was significantly higher in the GDM as compared to the Non-GDM group [UAs, µg/l, M±SD (range), 204.2±67.0 (67.0-377.0) vs 77.3±38.1 (22.0-99.0), p<0.001]. Pearson's correlation analysis showed nearly significant positive association of urinary arsenic with FBS (mmol/l) (r= 0.218, p= 0.053) and serum insulin (µIU/mL) (r=0.282, p=0.012) and negative association was found between urinary arsenic level (µg/l) with HOMA%S (r= -0.266, p=0.018). Multiple linear regression analysis also confirmed Urinary Arsenic level positively associated with HOMA%IR (β = 0.104; p=0.035) and inversely with HOMA%S (β= -0.036; p= 0.044) when (Age, 2 hr after blood glucose level, HDL, Insulin) was adjusted.

Conclusion: Urinary arsenic probably represent a potential causal association with insulin resistance; it may also provide clues to long-observed health disparities that have been associated with GDM.

Keywords: Arsenic Exposure; Gestational Diabetes Mellitus; Insulin Sensitivity

Introduction

Chronic arsenic exposure is associated with a number of adverse health effects [1]. Accumulating evidence has shown an increased risk of type 2 diabetes in general populations exposed to arsenic, but little is known about exposures during pregnancy and the association with gestational [2]. Suggestive evidence links chronic exposure to high arsenic levels in drinking water with increased diabetes risk in Taiwan and Bangladesh [3].

Exposure during pregnancy was associated with increased risks of morbidity (e.g. diarrhea) among pregnant women [3] pregnancy complications [4] as well as infant mortality [4,5] and morbidity (e.g. respiratory infection) (Ahmad et al. 2001, Rahman et al. 2011). The uncovering of increasing number of adverse effects due to maternal As exposure shows that it is an emerging public health problem in Bangladesh [6]. Arsenic-induced diabetes may occur through induction of insulin resistance and beta-cell dysfunction by arsenic (or its methylated metabolites) via induction of oxidative stress or interferences in signal transduction or gene expression [7]. Individual factors (e.g., nutritional status, genes) may also influence arsenic toxicity [8].

Although recently more attention has been focused on the reproductive health effects of arsenic, but these findings are still inconclusive [8,9]. Few studies have explored the effects of arsenic on human pregnancy outcomes [8,9,10] and none have investigated risk of diabetes in pregnant women, even though diabetes is a major potential complication of pregnancy with adverse effects for both mothers and infants. In this context, the cross sectional study was performed to determine whether as contamination is associated with insulin resistance during pregnancy.

Methodology

It was an observational cross sectional study. The study comprised face to face interview and urine, blood and house hold water sample were analyzed. This study was conducted in a rural upazilla of the People's Republic of Bangladesh, Chandina, Comilla selected as arsenic contaminated area. This district was selected based on evidence of presence of arsenic (As) contaminated tube wells. Databases from the local public health offices recorded 79% of tube wells with As levels higher than 50 μg/L. These records were provided to the NGO and district civil surgeon's Office, 2013. Total 79 pregnant mothers at 24-28 wks of gestation were enrolled in this study. Among them 38 were GDM and 41 were non-GDM pregnant mothers. Gynecologists of each centre conducted health checks for pregnancy complications such as preeclampsia, intrauterine growth retardation, placenta previa, and placental abruption; medical history such as diabetes mellitus; and neonatal outcome was assessed by a Specialist Clinicians. Informed consent was taken from each subject (fulfilling the inclusion criteria) in an appropriate form. In addition source and daily consumption of drinking, cooking water and information of previous pregnancy outcomes also recorded. Degree of chronic arsenic exposure was assessed by the level of As in the usable (drinking, cooking, washing) water at the respective households. Urinary & Serum-As was measured by inductively coupled plasma-mass spectrometry and adjusted with specific gravity ($U\text{-}As_{SG}$). (Agilent 7500cc-Agilent Technology, Hachioji, Japan). Level of significance calculated by student't' test for continuous value and n(%) was categories data by Chi square test. Correlation of Arsenic level and with other related variable by coefficient correlation analysis by Pearson's correlation. Dependant variable was arsenic level with other associated variable was calculated by multiple regression analysis.

Results

Out of the 79 pregnant women enrolled in this study, 38 were GDM and 41 were Non GDM GDM was diagnosed by DIPSI, 2013 Guideline. The cutoff point using 2hr after 75 gm glucose value was >7.7 mmol/L. The Serum Fasting glucose value (mmol/l, M±SD) were higher in GDM subjects (5.8±2.38) compare to the Non-GDM subjects (5.27±0.68), but not significant (p=0.183). The Serum 2 hr after 75 gm glucose value (mmol/l, M±SD) showed significantly higher in GDM subjects (9.67±3.70) compared to the Non-GDM subjects (6.4±0.90), ($p<0.001$). Serum Insulin (μIU/mL ,M±SD) also was significantly higher in GDM subjects (25.9±12.1) as compared to the Non-GDM subjects (11.39±9.92), ($p<0.001$). The Insulin sensitivity HOMA % S (M±SD) was

Results and Observations

Characteristic	GDM (n=38)	Non GDM (n=41)	P value
Age			
- Less than or equal to 23 Years	17 (44.73%)	25 (60.97%)	0.179
- Above 24 Years	21 (55.27%)	16 (39.03%)	
Education			
-Completed primary school(5)	23(60.53%)	27(65.86%)	0.632
-Completed secondary school(4)	11(28.94%)	12(29.27%)	
-Completed higher secondary school or above (3)	04(10.53%)	02(4.87%)	
Occupation			
- Housewife	37 (97.37%)	41 (100%)	0.481
- Service	01 (2.63%)	00 (00%)	
Family Member			
- Less than or equal to 4 member	22 (57.89%)	20 (48.78%)	0.501
- More than 4 member	16 (42.11%)	21 (51.22%)	
Monthly Income			
- Middle Income	28 (73.68%)	30 (73.17%)	1.000
- Upper Middle Income	10 (26.32%)	11 (26.83%)	
Color of Tube well			
- Red (1)	20 (52.63%)	16 (39.02%)	0.031
- Green(2)	06 (31.58%)	13 (29.07%)	
- Not defined (3)	12 (15.9%)	12 (31.01%)	
Duration of Water intake			
- Less than or equal to 01 year	09(23.68%)	07(17.07%)	0.784
- More than 01 Year	29(76.32%)	34(82.92%)	
Menstrual history			
- Regular (1)	33(86.84%)	38(92.68%)	0.346
- Irregular(2)	05(13.16%)	03(7.32%)	
Para			
- Primi	21(55.26%)	24(58.54%)	0.823
-Multi	17(44.74%)	17(41.46%)	
Family history of Diabetes Mellitus			
-No	35(92.10%)	35(85.36%)	0.484
-Yes	03(7.90%)	06(14.64%)	

Results are expressed as number and (percentages, %) n= number of subjects. The significance difference was analyzed by cross tab chi squire test. Significance level were calculated $p<0.05$.

Table 1: The socio-demographic status of GDM & Non GDM subjects

Characteristic	GDM mean± SD	Non-GDM mean± SD	P value
Age (yrs)	24.05±4.41	23.21±4.51	0.410
BMI (kg/m2)	22.90±5.13	23.09±3.38	0.848
SBP (mm of Hz)	105.52±11.07	105.12±10.27	0.867
DBP(mm of Hz)	69.21±7.49	68.04±8.13	0.512
S Fasting glucose value (mmol/l)	5.8±2.38	5.27±0.68	0.183
S 2 hr after 75 gm glucose value (mmol/l)	9.67±3.70	6.4±0.90	<0.001
S. Total Cholesterol (mg/dl)	198.94±39.16	199.29±26.95	0.963
S. Triglyceride (mg/dl)	202.92±75.04	220.14±89.81	0.360
S HDL- Cholesterol (mg/dl)	46.89±4.73	46.14±4.23	0.461
S LDL- Cholesterol (mg/dl)	117.21±33.48	111.31±20.70	0.346
S Insulin (µIU/mL)	25.9±12.1	11.39±9.92	**<0.001**
HOMA % S	65.37±26.64	192.44±92.48	**<0.001**
HOMA IR	3.08±1.86	1.27±0.999	**<0.001**
S. As level (µg/L)	2.3±1.8 (1.00-8.00)	2.1±2.4 (1.00-13.0)	0.595
U- As level (µg/L)	204.2±67.0 (67.0-377.0)	77.3±38.1 (22.0-99.0)	**<0.001**

Results were expressed as mean± *SD and* median (range), n= number of subjects. HTN=Hypertension, BMI=Body Mass Index, SBP=Systolic Blood pressure, DBP=Diastolic Blood Pressure. *S. LDL-Serum Low density of lipoprotein, HDL-High density of lipoprotein*

Table 2: The clinical and biochemical characteristics of GDM and Non-GDM subjects

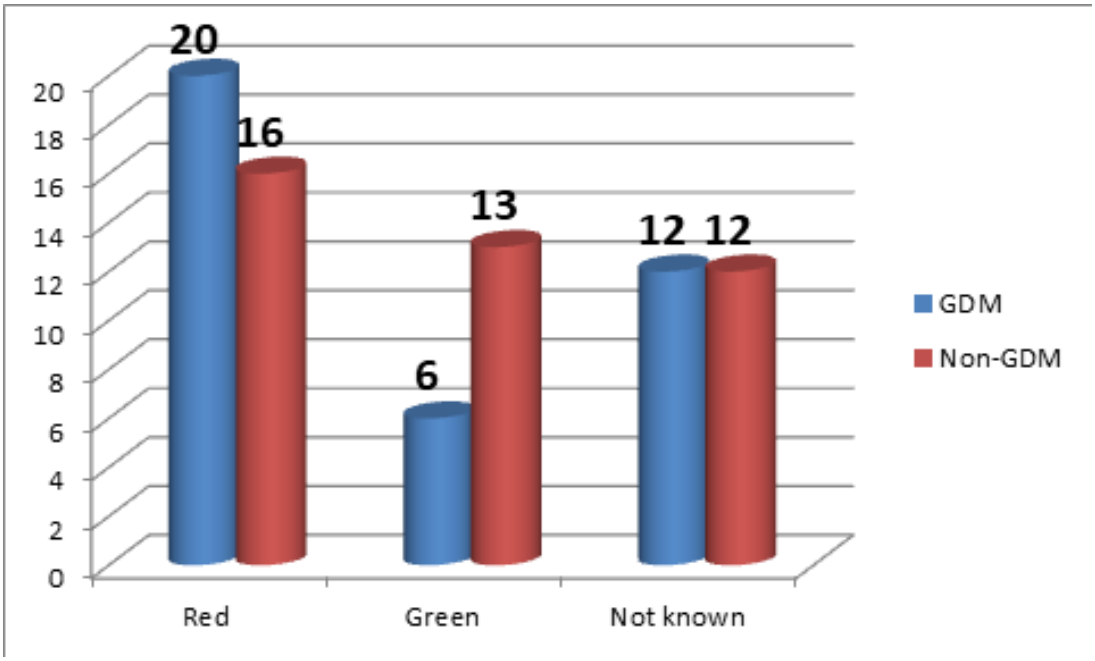

Figure: The proportion of using water sources of the study subjects.

Variables	GDM subjects (n=38)		Overall subjects (n=79)	
	r	p	r	p
Age (Yrs)	**0.711**	**0.062**	0.144	0.207
Para	0.168	0.313	0.172	0.129
BMI (Kg/m^2)	**0.900**	**0.021**	0.009	0.939
SBP (mm of Hz)	-0.241	0.145	-0.033	0.770
DBP (mm of Hz)	-0.096	0.568	0.054	0.638
FBS (mm of Hz)	0.073	0.664	0.102	0.370
After 75 gm Glucose (mg/dl)	0.231	0.162	0.218	**0.053**
Triglyceride (mg/dl)	-0.194	0.244	-0.059	0.606
Cholesterol (mg/dl)	0.092	0.585	0.032	0.782
HDL (mg/dl)	0.064	0.702	0.050	0.661
LDL (mg/dl)	**0.342**	**0.036**	0.198	0.080
Serum Insulin (mg/dl)	0.130	0.435	0.282	**0.012**
HOMA%S	**-0.619**	**0.043**	**-0.266**	**0.018**
HOMA IR	**0.153**	**0.036**	0.037	0.748

Results are expressed as Pearson's parametric correlation coefficient's analysis.

Table 3: Correlation of Urinary Arsenic level with other confounding variables

Variables	GDM		Overall	
	r	p	r	p
Age	0.082	0.625	-0.085	0.455
Para	-0.100	0.549	-0.070	0.542
BMI	-0.051	0.761	-0.022	0.847
SBP	0.059	0.727	-0.041	0.721
DBP	-0.011	0.949	-0.134	0.239
FBS	0.431	0.007	**0.198**	**0.081**
After 75 gm Glucose	0.293	0.074	0.115	0.311
Triglyceride	0.064	0.702	-0.147	0.197
Cholesterol	-0.032	0.850	-0.032	0.778
HDL	-0.237	0.152	0.092	0.422
LDL	-0.076	0.651	-0.071	0.533
Serum Insulin	-0.198	0.233	-0.112	0.325
HOMA%S	-0.241	0.145	-0.053	0.642
HOMA IR	0.156	0.350	0.031	0.787

Table 4: Correlation of the Serum Arsenic level with other confounding variables

Variable	Unstandardized Coefficients		Standardized Coefficients	P Value	95% CI for B	
	B	Std. Error	Beta β		Lower Bound	Upper Bound
Age	6.929	10.737	0.133	0.523	-14.915	28.773
HDL	1.880	1.479	0.210	0.213	-1.129	4.889
Insulin	1.519	0.910	0.319	0.105	-0.333	3.371
HOMA%S	-0.015	0.088	-0.036	0.044	-0.194	0.164
HOMA%IR	-3.923	6.252	0.104	0.035	-16.642	8.796

Table 5: Association of Urinary Arsenic as a dependant variable with other parameters as explored by multiple regressions

significantly lower in GDM subjects (65.37±26.6) as compared to the Non-GDM subjects (192.44±92.4), ($p<0.001$). The Insulin Resistance HOMA IR (M±SD) was significantly higher in GDM subjects (3.08±1.86) as compare to the Non-GDM subjects (1.27±0.99), ($p<0.001$).

Serum arsenic level did not show significant differences between the GDM and Non-GDM subjects [S. As, μg/L, M±SD, median (range)], [2.3±1.8, (1.0-8.0)] vs [2.1±2.4, (1.0-13.0), p-0.595]. Urine arsenic level was significantly higher in the GDM subjects as compared to the Non-GDM subjects [U-As, μg/L, M±SD, median (range), [204.2±67.0, (67–377) Vs [77.3±38.1 (22.0-99.0), $p<0.001$]. In coefficient correlation analysis, urinary Arsenic level showed significant positive association with Age (yrs) ($r= 0.711$, $p= 0.062$); BMI ($r=0.900$,$p=0.021$); LDL (mg/dl) ($r= 0.342$, $p= 0.036$) respectively and negative association with HOMA%S ($r= 0.438$, $p=0.0.025$; $r= 0.619$, $p=0.043$) respectively in GDM subjects. Multiple linear regression analysis also confirmed that Urinary Arsenic level was positively associated with HOMA%IR ($\beta = -0.104$; $p=0.035$) and negatively associated with HOMA%S ($\beta= 0.036$; $p= 0.044$) when (Age, HDL, Insulin) variable was adjusted.

Discussion

In this cross-sectional study, we evaluated that the association between markers of As exposure and Insulin resistance during pregnancy. Our results suggest that statistically significant positive association between urinary As with Insulin resistance in GDM subjects. Suggestive evidence links chronic exposure to high arsenic levels in drinking water with increased diabetes risk in Taiwan and Bangladesh [11].

This study demonstrated that Urine arsenic level was significantly higher in the GDM subjects as compared to the Non-GDM subjects [U-As, μg/L, M±SD, median (range), [204.2±67.0, (67–377) Vs [77.3±38.1 (22.0-99.0), $p<0.001$]. NHANES (National Health and Nutrition Examination Survey) data suggested that very low level of average total arsenic concentration in urine (8.30 μg/L) (95% CI, 7.19–9.57) [12].

Among this population of pregnant women with relatively high exposure, arsenic contamination was found to be associated with glucose intolerance during pregnancy and therefore may be associated with increased risk of GDM. In this study Coefficient correlation analysis also provided significant positive correlation between urinary arsenic level (μg/L) with Age (yrs) ($r= 0.711$, $p= 0.062$); BMI ($r=0.900$,$p=0.021$); LDL (mg/dl) ($r= 0.342$, $p= 0.036$) and HOMA IR ($r= 0.153$, $p=0.036$) respectively and negative relationship between urinary arsenic level (μg/L) with HOMA%S ($r= 0.438$, $p=0.0.025$; $r= 0.619$, $p=0.043$) respectively in GDM subjects. Vahter et al (2006) claimed that, higher arsenic concentration is associated with gestational diabetes mellitus and pregnancy complications. Ettinger et al, (2009) also found that the highest quartile of maternal blood As at delivery was associated with impaired glucose tolerance at 24–28 weeks of gestation (OR: 2.8, 95 % CI: 1.1, 6.9).

Several studies with animals and cells have proposed that arsenic may affect non-pancreatic tissues and induce insulin resistance via inhibitions of insulin signaling, the glucose transport system and the differentiation of pre-adipocytes to adipocytes and myoblasts to [13]. In this study in multiple linear regression analysis a negative association was found between urinary arsenic

and insulin resistance. (HOMA%IR (β = -0.104; p=0.035). Park et al. (2016) also reported a trend of positive correlation between urinary arsenic levels and HOMA-IR among study subjects recruited from the Amish Family Diabetes Study. On the contrary [14] did not find any association of arsenic exposure with insulin resistance in adolescent subjects [15-20].

In summary, GDM is a major potential complication of pregnancy associated with negative health effects for both the mother and infant. [21-25] Understanding the effects of environmental exposure on impaired glucose tolerance during pregnancy may have substantial public health importance beyond the direct effects on GDM. Studies are needed to investigate environmental, behavioral and biological factors that may contribute to risk for development and progression of diabetes and its related maternal complications. The above findings imply that arsenic contamination may play a role in glucose intolerance and may associate with an increased risk of GDM. [25-30] Finally, we conclude that urinary arsenic is probably representing a potential causal association with insulin resistance, it may also provide clues to long-observed health disparities that have been associated with GDM.

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