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• Original Article

Evaluation of different types of arsenic methylation and its relationship with metabolic syndrome in an area chronically exposed to arsenic

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Evidence suggests that the relationship between arsenic metabolism and diseases, including metabolic syndrome, is complex. The aim of this study was to evaluate the different types of arsenic methylation and its association with metabolic syndrome in an arsenic endemic area. A cross-sectional study was conducted on 132 subjects from Shahid-Abad Village, Qazvin province, Iran (arsenic endemic area). Demographic characteristics, metabolic syndrome, and urinary arsenic species, including iAs (inorganic arsenic), MMA (monomethylarsonic acid), and DMA (dimethylarsinic acid) were measured for all patients and their relationship was analyzed by appropriate statistical methods. In this study, 34.5% of the participants had metabolic syndrome. The decrease in %MMA, increase in %DMA and increase in secondary methylation index (DMA/MMA) were associated with increased risk of metabolic syndrome ($p<0.05$). We did not find any association between the incidence of metabolic syndrome with primary methylation index (MMA/iAs) and %iAs ($p>0.05$). This study showed that the prevalence of metabolic syndrome was significantly higher in people with metabolic syndrome than in the general population. A closer examination revealed that the secondary methylation index is related to the metabolic syndrome and its components. Given the higher prevalence of cardiovascular disease and diabetes in patients with metabolic syndrome, it is necessary to change the pathogenesis of the disease using comprehensive management methods for decreasing patient complications.

Keywords: arsenic toxicity, metabolism, diabetes, glucose, metabolic syndrome

Introduction

Heavy metals are one of the most important environmental pollutants whose rate of entry into water resources is increasing through agricultural, industrial and urban development activities [1-3]. Among heavy metals the inorganic arsenic (iAs) is a carcinogen that ranks the 20th in terms of frequency of elements in the earth's crust with an average of 1.8 mg/kg. It is naturally found in the oxidation state of AsV (arsenate) and AsIII (arsenite), the latter being about 60 times more toxic than the former [4].

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The biotransformation pathway of As involves several changes in oxidative state, oxidative methylation, and production of at least four metabolites. When this metalloid enters the body, iAs is metabolized from arsenate to arsenite and then metabolized by oxidative methylation to monomethyl arsenic (MMA). After the conversion from arsenate to arsenite, at the final methylation stage, dimethylarsinic acid (DMA) is produced [5, 6]. After exposure to arsenic, 40-60% of absorbed arsenic is eliminated by urine. Biological monitoring of arsenic exposure has been carried out for many years based on the determination of methylated metabolites, DMA and MMA, in urine [6].

This toxic metalloid is associated with an increased risk of complications, including cardiovascular consequences. Arsenic exposure is also related to the diagnosis of metabolic syndrome [7,8]. Metabolic syndrome is associated with a number of risk factors including abdominal obesity, hypertension, high triglycerides, and low high-density lipoprotien (HDL)

cholesterol, all of which occur together and increase the risk of heart disease, heart attack, and diabetes. Having only one of the symptoms listed above is not indicative of metabolic syndrome but can lead to other serious diseases [9,10]. Evaluation of this syndrome and its associated diseases is essential because significant lifestyle changes can prevent or at least delay the onset of related diseases [9-11].

A study in an industrial area in Taiwan shows that iAs was associated with the incidence of metabolic syndrome, increased plasma glucose, and increased blood lipid [12], but few studies have examined the effect of arsenic methylation on heart disease and metabolic syndrome [8,13]. The increasing evidence indicates that the relationship between arsenic metabolism and diseases, including metabolic syndrome, is complex [8,14,15]. On one hand, studies have shown that methylated arsenic is less toxic than inorganic form and that methylation is known as a detoxification reaction [16,17]. On the other hand, studies have shown that methylated arsenic has more cytotoxic and genotoxic effects than arsenate and arsenite [13, 18]. In addition to the cases noted, studies have indicated that interpersonal differences such as age, gender, genetics, and body mass index (BMI) are related to methylation capacity and metabolic syndrome, suggesting the necessity for conducting studies in different populations [19]. The goal of this study was to evaluate the different forms of arsenic methylation and its association with metabolic syndrome in an area with chronic exposure to arsenic through drinking water.

Materials and Methods

This is a cross-sectional study conducted in Qazvin University of Medical Sciences, Iran, in 2016. 132 subjects aged 24-90 years were recruited from Shahidabad village of Qazvin province, Iran, which is an endemic arsenic region. The concentration of arsenic in water wells in this region was about 257 to 342 μg/L. Inclusion criteria of subjects included chronic toxicity of arsenic examined by a clinical toxicologist and a written consent, and exclusion criteria of subjects included pregnancy, age (less than 20 years), and consumption of fish and/or seafood 48 hours before the test. Urinary arsenic species analysis including iAs, MMA, and DMA was performed using high-efficiency liquid chromatography with inductively coupled plasma mass spectrometry (HPLC-ICP-MS) (ICPMS-2030 Shimadzu device). After analyzing arsenic species, their percentages out of total arsenic were calculated as follows. %iAs=([iAs /total arsenic]×100), %MMA=([MMA/total arsenic]×100]) and %DMA=([DMA/total arsenic]×100).

A questionnaire examining demographic and clinical information was distributed among the patients. Data on age, sex, height, weight, smoking, and other client information were recorded. By height and weight data, BMI was calculated based on (kg/m^2). Waist circumference was also measured. All patients were examined by a physician and the necessary tests including fasting blood glucose, HDL-cholesterol and low-density lipoprotein (LDL) cholesterol were performed. Blood pressure was measured periodically using a graduated mercury sphygmomanometer with a precision of 2 mmHg after 5 min of rest. Fasting blood glucose was taken after twelve hours of fasting, followed by blood tests. Fasting blood glucose was measured by glucose oxidase method, lipid profile (triglyceride and total cholesterol) and HDL by immunocolorimetric assay, and LDL by Friedewald equation [20,21]. People with metabolic syndrome were considered as positive and otherwise as negative exposure.

Metabolic syndrome was diagnosed using the criteria suggested by the Third National Cholesterol Education Program (NCEP) report. In this method, the criteria for the diagnosis of metabolic syndrome having three or more than five criteria including waist circumference greater than or equal to 102 cm, hypertension (systolic ≥130 mmHg and diastolic ≥85 mmHg), triglycerides greater than or equal to 150 (mg/dL), HDL cholesterol greater than or equal to 40 (mg/dL), and fasting blood glucose greater than or equal to 100 mg/dL [22,23].

Anthropometric and laboratory data were analyzed for distribution. The data were provided using frequency and percentage for the categorical variables and mean and standard deviation for continuous variables. Independent t-test and chi-square tests were used to compare continuous and categorical variables, respectively. Logistic regression analysis was used to investigate the odds ratios of variables in metabolic syndrome. All statistical analyses were performed using SPSS software version 19 and p-value <0.05 was considered as significance level.

Results

Of the 132 arsenic exposed patients, 45 had metabolic syndrome and 87 had no metabolic syndrome. Table 1 shows the characteristics of clients based on different clinical and demographic factors. Age, BMI, blood pressure, blood glucose, triglyceride, HDL and waist circumference were significantly different in subjects with and without metabolic syndrome ($p<0.05$).

The occurrence of metabolic syndrome with regard to arsenic metabolites is presented in Table 2. The %iAs, %MMA, %DMA and secondary methylation index were significantly

different in the metabolic syndrome group with the group without the syndrome ($p<0.05$).

Table 3 presents the results of logistic regression analysis for the metabolic syndrome as the dependent variable. In this regression analysis, different forms of arsenic methylation were included as independent variables. In the raw analysis, a decrease in %MMA, increase in %DMA, and increase in secondary methylation index was associated with increased risk of metabolic syndrome. After adjusting for the regression model by age and BMI, although the odds ratios of the three variables mentioned were changed, there was no significant difference in their significance pattern.

Discussion

In this study, 34.5% of participants in the endemic arsenic region had metabolic syndrome. The prevalence of metabolic syndrome in this study was higher than the general population of Iran. In the meta-analysis performed by Maleki et al., the prevalence of metabolic syndrome in men was estimated to be about 20% [25]. A closer investigation in the present study revealed that decreasing %MMA, increasing %DMA, and increasing secondary methylation index were associated with an increased risk of metabolic syndrome. We did not report any relationship between the incidence of metabolic syndrome with primary methylation index and % iAs. These results are in line with that of Chen et al., which showed that low initial methylation was associated with a higher risk of metabolic syndrome [13]. In addition, a meta-analysis conducted in 2012 found a significant relationship between arsenic exposure and hypertension [26].

Given the arsenic concentration in the water well of this region (257 to 342 μg/L), such results were expected. Research in this regard has shown that consuming arsenic-contaminated water resources and the process of arsenic biotransformation in the liver can significantly increase the presence of arsenic metabolites and provide an opportunity for the generation of reactive oxygen species (ROS) [18,27]. On the other hand, oxidative stress and metabolic syndrome are also correlated [10] and this may be a rational justification for these results.

Several studies have shown a significant association between

Table 1. Status of metabolic syndrome according to demographic and clinical characteristics

Variable	Metabolic Syndrome (%)		p-value
	Yes	No	
Age (yr)	59.35±14.76	45.09±17.57	<0.001
Sex			
Female	33 (31.7)	71 (68.3)	0.27
Male	12 (42.9)	16 (57.1)	
Smoking	22 (32.8)	45 (67.2)	0.757
Education level			
Illiterate and elementary school	29 (41.4)	41 (57.6)	0.16
Secondary and high school	15 (26.3)	42 (73.7)	
University degree	1 (20)	4 (80)	
BMI (kg/m^2)	27.14±3.88	22.74±4.67	<0.001
Metabolic Syndrome Variables			
Systolic blood pressure	135.42±4.18	127.18±4.05	<0.001
Diastolic blood pressure	88.55±1.25	84.90±1.74	<0.001
Blood glucose	122.84±19.01	96.98±26.81	<0.001
Triglyceride	159.57±43.90	106.08±36.52	<0.001
HDL	34.77±6	44.19±15.04	<0.001
Waist circumference	90.20±7.78	81.06±7.87	<0.001

BMI=Body mass index; HDL=High-density lipoprotein cholesterol.

Table 2. Relationship between arsenic metabolites and metabolic syndrome

Variable	Metabolic Syndrome		p-value
	Yes	No	
iAs III (μg/L)	2.32±0.27	2.36±0.20	0.43
iAs V (μg/L)	0.69±0.03	0.74±0.24	0.14
iAs (μg/L)	3.01±0.29	3.10±0.37	0.15
MMA (μg/L)	2.90±0.35	3.12 ±0.9	0.06
DMA (μg/L)	15.53±3.55	14.15±4.53	0.07
%iAs	14.45±2.65	14.46±5.25	0.017
%MMA	13.69±0.99	15.33±2.52	<.0001
%DMA	71.85±3.32	68.19±5.50	<0.001
MMA/iAs	0.97±14	0.99±0.25	0.45
DMA/MMA	5.28±0.62	4.59±1	<0.001

iAs=inorganic arsenic; iAsV=5 capacity arsenic; iAs III=3 capacity arsenic; MMA=monomethyl arsenic; DMA=dimethylarsinic acid; %iAs=([iAs/total arsenic]×100; %MMA=([MMA/total arsenic]×100), %DMA=([DMA/total arsenic]×100); All values are based on the mean and standard deviation.

Table 3. Regression analysis to investigate the relationship between arsenic methylation pattern and metabolic syndrome (dependent variable)

Parameter	metabolic syndrome A			metabolic syndrome B		
	β	Odds ratio (95% CI)	p-value	β	Odds ratio (95% CI)	p-value
%iAs	-0.13	0.87 (0.77-0.98)	0.28	-0.09	0.9 (0.75-1.08)	0.27
%MMA	-0.36	0.69 (0.57-0.84)	<0.001	-0.27	0.76 (0.59-0.97)	0.03
%DMA	0.206	1.22 (1.09-1.37)	<0.001	0.17	1.18 (1.07-1.39)	0.04
MMA/iAs	-0.52	0.59 (0.11-2.97)	0.524	-0.92	0.39 (0.04-3.73)	0.41
DMA/MMA	0.85	2.35 (1.50-3.38)	<0.001	0.62	1.86 (1.05-3.31)	0.03

A is unadjusted metabolic syndrome without; B Metabolic syndrome adjusted for age and BMI.
iAs=inorganic arsenic; MMA=monomethyl arsenic; DMA=Dimethylarsinic acid; %iAs=([iAs/total arsenic]×100); %MMA = ((MMA/total arsenic)×100); %DMA = ([DMA/total arsenic]×100).

exposure to arsenic and triglycerides [28,29] and high-density lipoprotein cholesterol [30,31]. Contrary to our findings, in a study by Wang et al. [32], a positive relationship was found between total arsenic and metabolic syndrome. Few studies have emphasized the role of partial arsenic methylation in hypertension and heart disease [16,17], and this is inconsistent with the findings of the present study. This may be due to individual differences and differences in arsenic methylation capacity. A Study has shown that age, sex, genetics, and BMI influence methylation capacity [19]. This study examined demographic factors (age, sex, BMI, and education) in the two groups of metabolic syndromes. The results showed that among these factors only BMI and age were significantly different between the two groups, so the effects of these two variables were adjusted in the regression model, which was not significantly different from the original model.

In this study, one of the exclusion criteria was pregnancy. This choice was because pregnancy could affect the metabolic syndrome evaluation process. Pregnant women have different waist circumference, blood pressure, and cholesterol than other people. In pregnant women, %DMA increases with the progress of pregnancy as fat increases and this change may alter the patterns of arsenic metabolism [33]. In addition, subjects less than 20 years old were excluded. Evidence suggests that arsenic metabolism in subjects less than 20 years old is different from that in the other age group. In addition, metabolic syndrome in this age range is rare [7]. Another criteria of this study was the non-consumption of fish and seafood 48 hours before the test. Studies in this field show that seafood is commonly considered as a source of arsenic compounds. This may alter the urinary excretion of metabolites [34,35]. The arsenic species in the diet may lead to overestimation of exposure, therefore we excluded participants who ate fish and/or seafood 48 hours prior to the experiment.

In addition, identifying different arsenic species in this study was performed by high-quality laboratory methods such as HPLC-ICP-MS. This type of biological monitoring makes it possible to evaluate exposure to all sources and consider the estimates of available organic forms resulting from foods that sometimes increase concentrations up to 200 μg/L, which is one of the strengths of the present study.

One of the limitations of this study is its cross-sectional nature. This study design interprets the relationship between variables but does not determine the causal relationship among variables. Another limitation of the study was investigating this relationship in an arsenic-exposed area. To generalize these results to a larger population, prospective studies should be conducted considering the large sample size in different regions.

Conclusion

Our findings confirmed previous evidence that arsenic has effects on the metabolic syndrome and may increase the high burden of this syndrome in the arsenic-exposed population. In addition, our results showed that decreasing %MMA, increasing %DMA and increasing secondary methylation index was associated with increased risk of metabolic syndrome. However, we did not find out any relationship between the incidence of metabolic syndrome with primary methylation and % iAs. We suggest that future studies examine the effects of seafood consumption on this relationship. The use of such a methodology can better identify cardiometabolic complications. In addition, individual differences in arsenic methylation will be better demonstrated.

Conflic of Interest

none

CRediT Author Statement

AMK: Methology, Visualization, Concepualization, Investigation, Software, Data Curation Writing - Original Draft; AAS: Conceptualization, Methodology, Software, Visualization, Investigation, Supervision, Writing - Reviewing and Editing; HM: Conceptualization, Writing – Reviewing & Editing SK: Data Curation; MA: Data Curation.

Consent and Ethical Approval

This study was approved by the Ethics Committee of Qazvin University of Medical Sciences and the participation of individuals was subject to a written consent.

Competing Interests

The authors declare that they have no competing interests.

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