Exposure to inorganic arsenic and hypertension among non-diabetic Mexican women

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Abstract

Objective. To assess the association between hypertension (HTA) prevalence and the urinary levels of inorganic arsenic (iAs) and its metabolites in north Mexican women without type 2 diabetes mellitus (T2DM). **Materials and methods**. We included 150 self-reported hypertensive women without T2DM, matched by age with 300 women without diagnosis of HTA and T2DM. Women were interviewed regarding lifestyle, sociodemographic, and clinical characteristics. Urinary iAs metabolites were measured by high performance liquid chromatography inductively coupled plasma mass spectrometry, and methylation efficiency parameters were estimated. Unconditional logistic regression models were used to evaluate the associations. **Results.** Total arsenic minus arsenobetaine concentrations in urine varied from 0.57 to 303.29 µg/L, with a median of 12.90 µg/L. The adjusted model showed a significant negative association between HTA prevalence and monomethylarsonic acid (MMA) percentage (OR T3 vs. T1: 0.52; 95%CI: 0.31,0.86; p for trend: 0.03) and a significant positive association with the secondary methylation index (OR T3 vs. T1: 1.94; 95%CI: 1.17,3.22; p for trend: <0.01). **Conclusions.** We suggest that arsenic metabolism played an essential part in these associations and recognize the need to elucidate underlying mechanisms.

Keywords: hypertension; arsenic; metabolism; women; Mexico

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Resumen

Objetivo. Evaluar la asociación entre la prevalencia de hipertensión arterial (HTA) y los niveles urinarios de arsénico inorgánico (iAs) y sus metabolitos en mujeres del norte de México sin diabetes tipo 2 (T2DM). **Material y métodos**. Se incluyeron 150 mujeres con HTA autorreportada y sin T2DM, pareadas por edad con 300 mujeres sin diagnóstico de HTA y T2DM. Se entrevistaron a las mujeres sobre características de estilo de vida, sociodemográficas y clínicas. Los metabolitos urinarios de iAs se midieron por cromatografía líquida de alta resolución acoplada a espectrometría de masas con plasma acoplado inductivamente y se estimó la eficiencia de la metilación. Se utilizaron modelos de regresión logística no condicionada para evaluar las asociaciones. **Resultados.** Las concentraciones de arsénico urinario total menos arsenobetaína variaron de 0.57 a 303.29 µg/L, con una mediana de 12.90 µg/L. El modelo ajustado mostró una asociación negativa significativa entre la prevalencia de HTA y el porcentaje de ácido monometilarsónico (MMA) (RM T3 vs. T1: 0.52; IC95%: 0.31,0.86; p de tendencia: 0.03) y una asociación positiva significativa con el índice de metilación secundario (RM T3vs. T1: 1.94; IC95%: 1.17,3.22; p para la tendencia: <0.01). **Conclusión.** Se sugiere que el metabolismo del arsénico representó un papel esencial en estas asociaciones y se reconoce la necesidad de elucidar los mecanismos subyacentes.

Palabras clave: hipertensión; arsénico; metabolismo; mujeres; México

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Ingestion of water polluted with inorganic arsenic (iAs) in Argentina, Bangladesh, India, China, Chile, United States of America (USA), Mexico and other countries represents a public health problem.[1] Metabolism of ingested iAs involves reduction, oxidation, and methylation reactions; subsequently it is eliminated in the urine, mainly as dimethylarsinic acid (DMA) [60-70%], and to a lesser extent as monomethylarsonic acid (MMA) [10-20%], and iAs [10-30%], but proportions could differ due to factors such as iAs exposure level, age, sex, body mass index (BMI), smoking, alcohol intake, genetic polymorphisms in iAs metabolism, and nutrient consumption.[2,3] The metabolism of iAs has been differentially correlated with health effects; a higher percentage of MMA (%MMA) was positively associated with skin lesions, cardiovascular diseases, and certain cancers, and negatively with type 2 diabetes mellitus (T2DM), metabolic syndrome, BMI, and hypertension (HTA).[4-6]

Cardiovascular diseases are the first cause of death worldwide, being HTA the main risk factor. In 2019, HTA prevalence was estimated as 32% in women and 34% in men between the ages 30-79[7] contributing to 235 million disability-adjusted life years, and nearly 11 million deaths.[8] In Mexico, HTA prevalence is 29.4%, and about half of the hypertensive individuals were unaware of their disease (43.9%), representing a challenge for early diagnosis and prevention.[9] High sodium and low potassium intakes, alcohol consumption, sedentarism, and obesity have been reported as risk factors, nonetheless, environmental factors have also been described.[10] A systematic review identified a significant positive trend in the association between arsenic exposure and HTA prevalence[11] and increased pulse pressure.[12]

The evidence regarding the relationships between HTA and iAs metabolism in humans is inconsistent. Cross-sectional studies conducted in Asia reported significant[13] and non-significant positive associations between HTA and %MMA.[14-18] A cross-sectional study performed in Mexico described a significant negative association between HTA and %MMA,[19] and prospective studies in Taiwan and USA reported similar results.[20,21] Given the pathophysiological mechanisms shared between HTA and T2DM, the relationships between these diseases are debated; notwithstanding, some studies have suggested that T2DM is a risk factor of HTA.[22,23] Some reports adjusted by T2DM this association,[14,20] reported a T2DM prevalence of 17.6 and 10.5%,[19,21] or did not present information on this regard.[15-18] Therefore, our objective was to assess the association between HTA prevalence and urinary levels of iAs and its metabolites in north Mexican women without T2DM.

Materials and methods

Study design

This is a secondary analysis of women included in the control group of a study of incident cases and population-based controls to evaluate genetic and environmental factors associated with breast cancer in the Mexican northern states of Chihuahua, Coahuila, Durango, Nuevo León, and Sonora from 2007 to 2011; comprehensive details about recruitment were previously described.[24] Briefly, controls were selected by the Master Sample Framework employed for the National Health Surveys, which provides a list of rural and urban households selected through probabilistic methods. The response rate was 99.7%. This study followed the principles of the Declaration of Helsinki, and its protocol was approved by the Ethics, Biosafety and Research Committees of the National Institute of Public Health (Mexico). All participants provided written informed consent. We excluded participants with urinary creatinine concentrations <20 mg/dL (n= 118)[25,26] or >300 mg/dL (n= 1),[27] and women with self-reported DM (n= 187). HTA cases were randomly matched by age (±5 years) with two controls; the final sample size for this study was 150 cases and 300 controls.

Interviews. Trained staff interviewed women about their reproductive, sociodemographic, clinical, and lifestyle characteristics. We measured weight and height to obtain BMI (BMI= kg/m^2), as well as waist and hip circumferences. Furthermore, we defined as non-cigarette smokers those women who had smoked less than 100 cigarettes in their lifetime and were not currently smoking, participants who had smoked at least 100 cigarettes in their lifetime and were currently smoking as current cigarette smokers, and women who had smoked at least 100 cigarettes in their lifetime and did not currently smoke were classified as former smokers. We also asked for alcohol consumption.

Self-reported hypertension. Hypertension cases were identified based on a positive response to the question: *Have you ever been diagnosed with hypertension?*

Arsenic determination. First morning urine samples were collected from each participant in sterile polypropylene containers. A 4 ml aliquot of urine was prepared in a Cryovial (Simport Scientific, Beloeil, QC, Canada) and stored frozen at or below -20 °C, and then at -70 °C at *Centro de Investigación y de Estudios Avanzados* of *Instituto Politécnico Nacional* (Cinvestav) in Mexico City. We determined urinary concentrations (μg/L) of arsenite

(As^{+3}), arsenate (As^{+5}), MMA^{+5}, DMA^{+5}, and arsenobetaine (AsB) by high performance liquid chromatography inductively coupled plasma mass spectrometry (HPLC-ICP-MS) in the Analytical Section of the Hazard Identification Core (University of Arizona), according to Gilbert-Diamond and colleagues.[28] Concentrations below the limit of detection (LOD) (AsB: 24.32%; As^{+3}: 19.26%; As^{+5}: 56.32%; MMA^{+5}: 1.95%; DMA^{+5}: 0.49%) were imputed by their corresponding LOD value (AsB: 0.08; As^{+3}: 0.15; As^{+5}: 0.41; MMA^{+5}: 0.12; DMA^{+5}: 0.12) divided by two (LOD/2).[29] We added up iAs (As^{+3} and As^{+5}), MMA^{+5} and DMA^{+5} concentrations to obtain urinary total arsenic (TAs) minus AsB. Inorganic As metabolism was assessed by %iAs, %MMA and %DMA based on TAs-AsB values, and methylation indexes: primary (PMI)= MMA/iAs; secondary (SMI)= DMA/MMA. Urinary creatinine concentrations (mg/dL) were quantified by spectrophotometry using a Randox Creatinine Kit, Antrim County, UK, according to Blanco-Muñoz and colleagues.[30] We estimated the variation coefficients: AsB: 18%; As^{+3}: 8%; MMA^{+5}: 8%; DMA^{+5}: 9%; creatinine: 2.76%.

Statistical analysis. Neighboring states of Durango (n= 31) and Coahuila (n= 100) had small sample sizes, so they were combined into a single group. Sociodemographic and clinical history features, and anthropometric measurements were described and compared between women with or without HTA, by Student *t* and χ^2 tests, as appropriate. Concentrations (adjusted and unadjusted for creatinine) of TAs, TAs-AsB, and iAs metabolites, along with their percentages related to TAs-AsB (μg/L) and metabolism parameters in HTA cases and controls were compared by Mann-Whitney U test.

We defined categories for TAs-AsB and iAs metabolites based on tertile distribution amid controls. Associations between HTA and TAs-AsB (adjusted for creatinine or μg/L) and iAs metabolism parameters were assessed by unconditional logistic regression models. We selected covariables based on minimally sufficient adjustment sets by Directed Acyclic Graphs using DAGitty v3.0 software,[31] which yielded age, smoking, and state of residence. Trend tests were performed with the corresponding continuous independent variables. We completed analyses using Stata 14 (Stata Corp, College Station, TX, USA).* Results were considered statistically significant at a *p*-value <0.05.

* StataCorp. Stata Stadistical Software 14. Collage Station, TX: StataCorp LLC, 2015.

Results

In our study population, TAs-AsB urine concentrations fluctuated from 0.57 to 303.29 μg/L with 12.90 μg/L as median (data not shown in tables). Compared with control women, HTA cases had similar years of residence in the study area, schooling years, a smaller proportion of individuals in the lower BMI categories, and significantly higher in the top category (>29.99), significantly higher waist to height ratio values, without significant differences in the waist to hip ratio. HTA women also showed a lower proportion of alcohol consumers without significant differences in the proportion of current cigarette smokers (table I).

No significant differences were observed in urinary creatinine and arsenic species concentrations (μg/L and μg/g creat) amid cases and controls. Regarding iAs metabolism parameters, HTA cases had significantly lower %iAs and %MMA, while %DMA and SMI were significantly higher than in control women (table II). After adjusting for age, smoking, and state of residence, a significant negative association was observed between HTA prevalence and %MMA ($OR_{T3\ vs.\ T1}$: 0.52; 95%CI: 0.31,0.86; *p* for trend:0.03). Furthermore, a significant positive association between HTA prevalence and SMI was observed ($OR_{T3\ vs.\ T1}$: 1.94; 95%CI: 1.17,3.22; *p* for trend <0.01) (table III).

Discussion

The negative association between prevalent HTA and %MMA, and HTA positive association with SMI, suggest that arsenic metabolism played a leading role in these associations. The non-significant associations between HTA and urinary total arsenic, or metabolite concentrations here reported, agreed with results from the USA in a cross-sectional study showing TAs values of 8.3 μg/L and ranging from 4.2 to 17.0 in the USA,[32] a prospective study with a median TAs urinary concentration of 6.5 μg/L,[21] and with a meta-analysis of prospective evidence.[33] However, a cross-sectional study in USA with a median urinary TAs concentration of 9.4 μg/L (interquartile range: 5.7, 16.1 μg/L) reported a positive significant association, which agreed with a previous meta-analysis that included studies with low (<50 μg/L) and moderate to high arsenic levels (≥50 μg/L) in drinking water.[11,34] To clarify the relationships between HTA and T2DM, future meta-analyses should report T2DM status of participants.

Previous studies where the relationships between iAs metabolites and HTA were adjusted by T2DM in multivariate analysis, showed inconsistent results since non-significant positive association between %MMA and HTA, at levels above 50 ppb of iAs in water were

Table I
General characteristics of study population from Northern Mexico, 2007-2011

Characteristics	*All (n= 450)*	*Cases (n= 150)*	*Controls (n= 300)*	*p value*
Age, (years) [Mean±SD]	57.86±11.54	57.89±11.60	57.85±11.53	0.97
Education (years), [%]				0.58
≤6	76.44	78.00	75.67	
>6	23.56	22.00	24.33	
State of residence, [%]				0.11
Nuevo León	27.11	20.00	30.67	
Coahuila	29.11	33.33	27.00	
Chihuahua	17.56	18.67	17.00	
Sonora	26.22	28.00	25.33	
Time of residence, (years) [Mean±SD]	51.13±13.86	52.59±14.05	50.40±13.73	0.12
Body mass index, (kg/m^2) [%]				**0.00**
<25	15.33	**10.67**	**17.67**	
25-29.9	32.44	**25.33**	**36.00**	
>29.9	52.22	**64.00**	**46.33**	
Waist-hip ratio, [Mean±SD]	0.91±0.07	0.92±0.07	0.91±0.06	0.26
Waist-height ratio, [Mean±SD]	0.65±0.08	**0.68±0.08**	**0.64±0.07**	**0.00**
Cigarette smoker, [%]				0.37
Non-cigarette smoker	71.56	68.67	73.00	
Former smoker	13.78	13.33	14.00	
Current cigarette smoker	14.67	18.00	13.00	
Alcohol consumption, [%]				0.25
No	92.67	94.67	91.67	
Yes	7.33	5.33	8.33	

Bold numbers correspond to statistically significant differences with a *P*-value <0.05

reported.[14,20] However, studies including diabetic patients without adjusting their data for T2DM, reported significant positive associations between HTA and urinary MMA concentration ($\mu g/g$), non-significantly positive with %MMA, significantly negative in the second tertile with %DMA with a geometric mean urinary TAs concentration above 135 $\mu g/g$ creat,[17] and null with %iAs, %MMA and %DMA.[21] Our findings agreed with the reported significant or marginally negative associations between %MMA and HTA with urinary TAs concentrations higher than those reported in this study,[19,20] the non-significant negative association between PMI and HTA,[13,16,18,19] and the positive association between HTA and SMI.[19] Nonetheless, cross-sectional studies observed a negative significant association between HTA and SMI,[13] and non-significant positive results.[16] The present study only included women, and since arsenic methylation is more efficient in them,[35,36] comparing our results with studies including both sexes is challenging. Further studies stratified by sex are needed to assess the contribution of sex-dependent methylation to these associations. The aforementioned contrasts with previous studies which reported %MMA was positively associated with cardiovascular diseases and some types of cancer, and negatively with metabolic diseases.

Experimental studies on cultured aortic and liver endothelial cells showed the mechanisms underlying the relationship between HTA and iAs,[37-39] but less information is available on arsenic metabolites with higher toxicity. Our results could be explained by MMA^{+3} dual effects, since high concentrations suppressed aortic phenylephrine-induced vasoconstriction, whereas lower levels potentiated vasoconstriction in damaged vascular tissue in rodents.[40] Studies using MMA^{+3} reported that inhibition of adrenergic induced blood vessel contraction resulting from permanent damage in smooth muscle function in arteries, lead to blood pressure changes.[41] Other experiments showed that iAs^{+5} and MMA^{+3} increased calcium sensitization in vascular smooth muscle cells leading to vasoconstriction[42] and MMA^{+3} inhibited endothelial nitric oxide synthase activity, reducing nitric oxide content and, triggering endothelial dysfunction in cells from human umbilical veins and bovine aortic artery.[43,44]

Some methodological issues should be considered when our results are interpreted. Self-report HTA prevalence in the original study (28.7%) was in agreement with the prevalence reported for women between 40 to 69 years of age in the Mexican National Health and Nutrition Survey.[45] Thus, it is likely that HTA prevalence in our study sample is a good estimator of that occurring in the target population. Regarding exposure assessment, an increase in As concentrations in water over the years due

Table II
Urinary arsenic species in the study population. Mexico

Arsenic metabolites	All (n= 450) Median (P10,P90)	Cases (n= 150) Median (P10,P90)	Controls (n= 300) Median (P10,P90)	p value
Concentration (µg/L)				
iAs	1.01 (0.28,5.57)	0.92 (0.28,4.82)	1.05 (0.28,6.23)	0.53
MMA	1.18 (0.30,5.99)	1.08 (0.24,6.08)	1.23 (0.32,5.97)	0.32
DMA	10.08 (2.67,48.63)	11.11 (2.70,54.54)	9.67 (2.65,43.28)	0.84
TAs-AsB	12.90 (3.61,59.51)	13.67 (3.76,67.44)	12.14 (3.51,55.21)	0.99
TAs	16.09 (4.00,87.82)	16.10 (4.05,87.84)	16.10 (3.98,87.82)	0.65
Concentration (µg/g creat)				
iAs	1.62 (0.57,7.72)	1.84 (0.59,6.99)	1.45 (0.54,8.50)	0.37
MMA	1.69 (0.54,8.05)	1.75 (0.53,7.09)	1.67 (0.56,8.46)	0.91
DMA	13.85 (4.64,59.66)	16.47 (5.12,55.44)	12.92 (4.57,64.15)	0.17
TAs-AsB	17.56 (5.88,73.98)	19.78 (6.45,69.41)	16.34 (5.73,78.63)	0.20
TAs	22.43 (6.52,126.20)	27.54 (7.19,139.71)	20.27 (6.39,122.46)	0.16
Proportions (%)				
iAs	9.19 (5.37,16.27)	**8.43 (4.59,17.46)**	**9.59 (5.59,15.95)**	**0.05**
MMA	9.86 (5.80,15.14)	**9.24 (5.16,14.97)**	**10.08 (6.39,15.19)**	**0.01**
DMA	80.53 (70.19,87.60)	**81.62 (70.14,88.17)**	**79.87 (70.19,86.58)**	**0.01**
Methylation indexes				
Primary	1.05 (0.58,1.86)	1.02 (0.54,1.94)	1.06 (0.61,1.82)	0.41
Second	7.98 (4.63,14.35)	**8.69 (4.67,17.03)**	**7.71 (4.58,12.94)**	**0.01**
Creatinine in urine (mg/dL)	71.74 (28.49,167.67)	67.23 (27.74,153.25)	73.71 (29.00,172.23)	0.17

Bold numbers correspond to statistically significant differences with a *P*-value <0.05
iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid; TAs: total arsenic; AsB: arsenobetaine

to prolonged droughts, aquifer overexploitation and other anthropogenic activities could not be ruled out.[46] Although it would be desirable to collect more than one urine sample to assess exposure and, methylation ability, a single sample of urine has been considered a good approximation of chronic exposure, considering that the main source of iAs was daily water intake.[47] Individual methylation patterns were reported to have daily small fluctuations (<5%).[48] However, due to potential random measurement error in iAs methylation capacity in arsenic determination, its association with HTA might be underestimated in this report. For subsequent studies, this limitation could be prevented by converting all As^{+3} to As^{+5}.[49]

In conclusion, the negative association with %MMA and the positive association with SMI suggested that an altered methylation capacity was associated with HTA. The differences in arsenic metabolite profile among various As-related diseases suggest the need to elucidate the underlying mechanisms.

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Table III
HYPERTENSION ODDS RATIOS IN RELATION TO INORGANIC ARSENIC METABOLISM. MEXICO

Inorganic arsenic metabolites	*Odds ratios (95%CI)*				
	Continuous	*Tertiles*			*P for trend*
		1st	*2nd*	*3rd*	
TAs-AsB (µg/L)					
N Cases/controls	150/300	52/100	51/100	47/100	
Model 1	1.00 (0.99,1.00)	1.00 (Reference)	0.85 (0.51,1.40)	0.67 (0.39,1.15)	0.48
TAs-AsB (µg/g creat)					
N Cases/controls	150/300	45/100	44/100	61/100	
Model 1	1.00 (0.99,1.00)	1.00 (Reference)	0.87 (0.51,1.48)	1.05 (0.61,1.82)	0.38
Arsenic metabolism					
% metabolites					
iAs					
N Cases/controls	150/300	68/100	40/100	42/100	
Model 1	1.00 (0.98,1.02)	1.00 (Reference)	0.63 (0.38,1.04)	0.61 (0.37,1.01)	0.95
MMA					
N Cases/controls	150/300	65/100	50/100	35/100	
Model 1	**0.94 (0.89,0.99)**	1.00 (Reference)	0.73 (0.45,1.17)	**0.52 (0.31,0.86)**	**0.03**
DMA					
N Cases/controls	150/300	43/100	38/100	69/100	
Model 1	1.01 (0.99,1.03)	1.00 (Reference)	0.94 (0.55,1.59)	1.61 (0.98,2.63)	0.38
Methylation indexes					
Primary methylation index					
N Cases/controls	150/300	62/100	35/100	53/100	
Model 1	0.89 (0.63,1.24)	1.00 (Reference)	**0.57 (0.35,0.95)**	0.82 (0.51,1.31)	0.49
Secondary methylation index					
N Cases/controls	150/300	36/100	47/100	67/100	
Model 1	**1.07 (1.02,1.11)**	1.00 (Reference)	1.28 (0.76,2.15)	**1.94 (1.17,3.22)**	**0.00**

Model 1 adjusted by age, smoking and state of residence
iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid; TAs: total arsenic; AsB: arsenobetaine
Bold numbers correspond to statistically significant differences with a *p*-value <0.05
Tertiles: TAs-AsB [µg/L] (≤8.41, >8.41-≤21.04, >21.04); TAs-AsB [µg/g creat] (≤10.84, >10.84-≤26.73, >26.73); %iAs (≤7.92, >7.92-≤11.75, >11.75); %MMA (≤8.71, >8.71-≤11.79, >11.79); %DMA (≤76.62, >76.62-≤82.24, >82.24); PMI (≤0.90, >0.90-≤1.29, >1.29); SMI (≤ 6.53, >6.53-≤9.22, >9.22)

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Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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