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Original Paper

Adjusting for Urinary Creatinine Overestimates Arsenic Concentrations in Diabetics

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Key Words
Arsenic · Creatinine · Diabetes · Insulin resistance · Specific gravity

Abstract
Background/Aims: Arsenic (As) is linked to insulin resistance in animal studies, but the effect of low-level As exposure on the prevalence of diabetes in humans is uncertain. An optimal method to report inorganic As in humans has not been established. Measurements of As in spot urine are usually adjusted to creatinine (Cr). However, urinary Cr is an independent variable in diabetes. Our aims are to optimize reporting of urinary As in the setting of diabetes and insulin resistance. ***Methods:*** Urinary inorganic As was measured in 24-hour or first-void spot urine from diabetic (n = 31) and non-diabetic (n = 12) subjects and normalized to Cr or specific gravity (SG). The relation of normalized urinary inorganic As to glycemia and surrogate measures of insulin resistance was investigated. Blood pressure, waist circumference, and glycated hemoglobin were also assessed. Homeostasis model assessment was used to determine insulin resistance. ***Results:*** A strong correlation was found between spot urinary As adjusted to Cr ($R^2 = 0.82$) or SG ($R^2 = 0.61$) to 24-hour urinary As ($p < 0.001$), while non-adjusted urinary As did not correlate well ($R^2 = 0.03$, $p = 0.46$). Adjusting for Cr revealed significant differences in total 24-hour urinary As when comparing diabetic to normal subjects. In contrast, no differences were found when

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As was adjusted to SG using either 24-hour or spot urine. Moreover, adjusted urinary spot or 24-hour As measures did not correlate with measures of glycemia or insulin resistance. ***Conclusions:*** Urinary Cr is an independent variable in diabetes, therefore adjusting spot As for SG is preferred.

Introduction

Inorganic arsenic (As) at relatively high concentrations is associated with increased glucose and insulin levels in animal models [1], decreased glucose uptake in insulin-sensitive cells [2], and interference with transcription factors involved in insulin signal transduction and insulin sensitivity in vitro [3]. Recently, particular attention was given to the relationship between low-level inorganic As exposure and type 2 diabetes in humans [4]. These data were obtained from analysis of spot urine samples from the National Health and Nutrition Examination Survey (NHANES) database, and urinary adjustments were based on urine creatinine (Cr). The NHANES study examined the relation of organic and inorganic As to measures of glycemia (glycated hemoglobin), but did not include measures of insulin resistance. Alternatively, a second analysis that excluded organic As [arsenobetaine (AsB)] [5] showed no association between low exposure of inorganic As and glycated hemoglobin. The authors questioned the use of urinary Cr as a confounding factor [5]. Urinary Cr is the most common biomarker used when adjusting urinary compounds for hydration status. However, it is also associated with muscle mass, meat intake, and adequacy of certain nutrients (folate/vitamin B_{12}) [6]. The suitability of urinary Cr in adjusting for urinary As excretion in the setting of diabetes is questionable since As may affect Cr metabolism [7, 8]. Diabetes alters kidney function and Cr clearance [9], although it is unknown if diabetes alters the excretion and metabolism of As. Specific gravity (SG), measured by refractometry, is another method to assess hydration status. The refraction increases with the total solute concentration in the urine. Samples with significant amounts of protein or glucose in urine may lead to erroneous results when adjusting for SG. The optimal method to report inorganic As has not been established. Moreover, no prior studies have examined the relation of inorganic As species to measures of insulin resistance in humans. Thus, the purpose of this study is (i) to define the optimal methods to report urine As measures in diabetes, and (ii) to study the relationship between inorganic As level and surrogate markers of insulin resistance and glycemia.

Methods

Subjects

A total of 49 volunteers (23 males and 26 females) provided 24-hour urine samples the day before, and plasma and spot urine samples on the morning of the study after overnight fasting. Subjects were selected from a larger representative cohort of subjects with and without diabetes recruited from southern Arizona, a region with a high prevalence of type 2 diabetes [10]. Approximately half of the participants were of Hispanic ethnicity and half were Caucasians. Subjects were recruited from diabetes and primary care clinics and by word of mouth. The level of inorganic As exposure was not well defined in our population. Most of the subjects reside in Tucson, Arizona, where the urban water is below the Environmental Protection Agency As water standard of 10 parts per billion (ppb), yet persons using private wells in rural areas can be exposed to elevated levels of As (e.g. >80 ppb). The study was approved by the University of Arizona Institutional Review Board. Spot urines were first void. Participants ingested a standard 75-gram glucose solution, and diabetes diagnosis was based on prior history or a 2-hour blood glucose ≥200 mg/dl. No information was obtained regarding seafood consumption in our subjects, which can affect AsB concentrations. Six subjects were excluded when urine Cr excretion was <800 mg in 24-hour samples, as

this reflects an inadequate 24-hour urine sample [11]. Four diabetic subjects had evidence of proteinuria and were excluded from SG-adjusted analysis [12]. Subsequently, results from 43 subjects were presented herein. Twenty-four-hour urine samples were stored in 20-ml polyethylene bottles, which were frozen within 6 h after sampling and kept at –80°C until analysis.

As Measures

Since the urine samples were not stored with preservative and the samples were collected over a period of time, it could not be guaranteed that the methylated As in the As III oxidation state had not decomposed. So a more conservative analysis was performed that has been used in past studies when urine samples were collected and stored over a substantial period of time [13]. The metabolites of inorganic As in urine [inorganic As (III), methylarsonic acid (MMA) (V), dimethylarsinic acid (DMA), inorganic As (V), and AsB, in ppb] were determined using inductively coupled plasma mass spectrometry [14]. The detection limit for AsB and DMA (V) was 0.14, for As (V) and As (III) it was 0.15 and for MMA (V) 0.11. As (V) was below the level of detection for a significant proportion of the cohort and was omitted from the analysis. Total inorganic As was calculated as the sum of As (III), DMA, and MMA. Urine Cr was determined by the Jaffé method [15] at an accredited clinical laboratory affiliated with the University of Arizona. SG was measured by refractometry. Urine As was adjusted for urine Cr by dividing the concentration of As metabolites with urine Cr (g/l). As was adjusted for the overall mean SG value of 1.016 of the total study group, according to: urine As × (1.016 – 1)/(measured SG – 1), as suggested by the National Institute for Occupational Safety and Health Benzene Criteria Document [12]. SG measurements were performed immediately after thawing of urine for As analysis. Based on experience from previous studies [16], freezing the urine samples does not change the SG ($r^2 > 0.95$). Glomerular filtration rate (GFR) was calculated according to the MDRD (Modification of Diet in Renal Disease) formula [estimated GFR (eGFR)] [17] and by the Chronic Kidney Disease Epidemiology Collaboration formula [18].

Biochemical Measures

Homeostasis model assessment of insulin resistance (HOMA-IR) based on the following formula [fasting insulin (IU/ml) × fasting glucose (mmol/l)/22.5] was calculated as previously described [19]. Weight, height, waist circumference, fasting lipids, glucose, insulin, HbA1c, serum Cr and urine microalbumin were measured in all subjects.

Statistical Analysis

Differences in As and biochemical measures between diabetic and non-diabetic groups were evaluated by non-parametric Mann-Whitney U test. Linear regression analysis was used for evaluation of the correlation associations between 24-hour and spot adjusted and unadjusted As measures. Concentrations of As (adjusted and non-adjusted) in urine, urinary Cr and SG were not normally distributed, and to meet the assumptions of normality in the ANOVA analysis, the concentrations were ln transformed. The analyses were performed with SPSS (Chicago, Ill., USA). A value of $p < 0.05$ was considered statistically significant.

Results

Subject Characteristics

A total of 43 subjects (12 subjects without diabetes and 31 subjects with diabetes) were studied. The diabetics did not significantly differ from non-diabetic subjects in measures of eGFR, plasma and urinary Cr, or SG. In addition to differences in glycemic control, diabetic patients had significantly elevated systolic blood pressure, waist circumference, fasting triglycerides and HOMA-IR compared to non-diabetics at baseline. The subgroup characteristics are summarized in table 1.

As Measures

Measures of organic and inorganic As (adjusted and unadjusted) in the diabetic and non-diabetic 24-hour urine samples are summarized in table 2. Unadjusted inorganic As in spot urine samples correlated poorly with 24-hour urinary As excretion (table 3). This con-

Table 1. Baseline characteristics of the subjects with and without diabetes

Characteristics	Non-diabetic group (n = 12)	Diabetic group (n = 31)	p value
Age, years	51 ± 16	58 ± 11	0.12
Male:female ratio	7:5	17:14	
Systolic blood pressure, mm Hg	117 ± 12[a]	131 ± 18[a]	*0.02*
Diastolic blood pressure, mm Hg	76 ± 8	77 ± 11	0.75
Body mass index	29.8 ± 5.8	39.6 ± 2.8	0.07
Waist circumference, cm	101 ± 16[a]	112 ± 13[a]	*0.02*
Fasting glucose, mg/dl	104 ± 14[a]	160 ± 63[a]	*0.003*
HbA1c, %	5.6 ± 0.5[a]	8.0 ± 2.6[a]	*0.008*
HOMA-IR	2.2 ± 1.4[a]	6.2 ± 4.9[a]	*0.005*
Triglycerides, mg/dl	119 ± 54[a]	213 ± 196[a]	*0.02*
HDL cholesterol, mg/dl	51 ± 10	48 ± 10	0.80
LDL cholesterol, mg/dl	106 ± 28	103 ± 31	0.78
Plasma Cr, mg/dl	0.84 ± 0.18	0.89 ± 0.26	0.60
eGFR MDRD, ml/min/1.73 m^2	91 ± 21.3	88 ± 21.2	0.40
eGFR CKD-EPI, ml/min/1.73 m^2	93.5 ± 28.5	83.6 ± 19.7	0.35
Urinary Cr, mg/ml	1.02 ± 0.45	0.79 ± 0.38	0.16
Urinary SG	1.015 ± 0.0015	1.017 ± 0.0012	0.48
Urine SG adjusted	1.24 ± 0.51	1.19 ± 0.53	0.70

Means ± SD. Non-parametric data were ln transformed. [a] $p < 0.05$. SG adjustment was based on the formula (1.016 – 1)/(measured SG – 1). CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

Table 2. Measures of adjusted and unadjusted arsenic in urine from subjects with and without diabetes

	Non-diabetic group (n = 12)	Diabetic group (n = 31)	p value
Non-adjusted As from 24-hour urine			
AsB	4.1 ± 4.7	19.2 ± 61.4	0.41
As (III)	0.42 ± 0.2	0.45 ± 0.2	0.75
DMA (V)	4.67 ± 1.6	5.7 ± 3.4	0.36
MMA (V)	0.61 ± 0.4	0.59 ± 0.3	0.88
Total inorganic As	5.3 ± 2.4	6.6 ± 3.9	0.27
SG-adjusted As in spot urine			
AsB	5.1 ± 6.1	20.1 ± 57.1	0.35
As (III)	0.44 ± 0.2	0.39 ± 0.18	0.45
DMA (V)	5.1 ± 1.5	5.5 ± 2.8	0.61
MMA (V)	0.7 ± 0.38	0.6 ± 0.41	0.53
Total inorganic As	5.7 ± 2.2	6.4 ± 3.2	0.52
Cr-adjusted As in spot urine			
AsB	4.7 ± 5.4	18.2 ± 4.6	0.60
As (III)	0.43 ± 0.22	0.51 ± 0.23	0.23
DMA (V)	4.81 ± 1.62[a]	7.0 ± 3.4[a]	*0.04*
MMA (V)	0.68 ± 0.41	0.75 ± 0.53	0.62
Total inorganic As	5.5 ± 2.3[a]	8.1 ± 3.9[a]	*0.01*

Means ± SD. Non-parametric data were ln transformed. As measures are in ppb, as previously defined. [a] $p < 0.05$. SG adjustment was based on the formula (1.016 – 1)/(measured SG – 1).

Table 3. Correlation between urinary levels of spot and 24-hour As

24-hour As	Unadjusted spot As		SG-adjusted spot As		Cr-adjusted spot As	
	R^2	p value	R^2	p value	R^2	p value
AsB	0.85	<0.001	0.90	<0.001	0.98	<0.001
As (III)	0.15	0.132	0.44	0.004	0.39	0.008
DMA (V)	0.06	0.28	0.63	<0.001	0.85	<0.001
MMA (V)	0.007	0.7	0.67	<0.001	0.86	<0.001
Total inorganic As	0.03	0.46	0.61	<0.001	0.82	<0.001

Data suggested that unadjusted spot urine inorganic As analysis poorly correlated with 24-hour urine As, highlighting the need to adjust for either Cr or SG.

trasts to a strong correlation between adjusted spot urine (to either urine Cr or SG) and 24-hour urinary As excretion. Spot urinary concentration of AsB strongly correlated (both adjusted and non-adjusted) to those in 24-hour samples. Age and sex did not correlate with urine As measures in the cohort.

Unadjusted and SG-adjusted inorganic As measurements did not significantly differ in subjects with versus without diabetes (table 2). In contrast, the total inorganic As and DMA (V) adjusted to Cr were significantly increased in diabetics compared to non-diabetic subjects ($p < 0.05$). The sample size showing at least a 20% difference between subjects in As measures with and without diabetes with a power of 0.8 was highly dependent on the method of adjustment. When adjusted for SG, a 10- and a 6-fold increase in sample size is needed to a show a statistically significant difference between diabetic and non-diabetic samples for DMA (V) and total inorganic As, respectively, compared to Cr adjustment.

Using simple linear regression, the correlation of measures of 24-hour As concentration was studied, As adjusted for either Cr or SG to HOMA-IR, waist circumference (surrogate measures of insulin resistance), and to glycated hemoglobin. A significant correlation between 24-hour urine As or spot urine As adjusted for Cr or SG and measures of glycemia or insulin resistance was not found.

Discussion

In this study, 24-hour urinary As analysis did not show a significant difference between diabetic and non-diabetic subjects. In addition, spot urine As measures were only strongly correlated with 24-hour urine As concentrations when adjusted for Cr or SG. Normalizing to urine Cr conveyed a stronger association with 24-hour As measures than normalizing to SG. However, adjusting for urine Cr produced significant differences between the diabetic and non-diabetic subjects for certain inorganic As species that were not observed when adjusting for SG or in the 24-hour As analysis. Therefore, urine Cr appears to be an independent variable in the setting of diabetes, which, when used for correction, overestimates the As differences between the diabetic and non-diabetic subjects. In a Bangladesh study on 1,466 adults [16], Cr excretion was found to be more dependent than urinary SG on body size, age, gender, and season. The authors concluded that urinary As would be greatly overestimated in children and/or malnourished individuals compared to older and/or better-nourished individuals if adjusted for Cr excretion. This observation was extended to subjects with diabetes where alterations in kidney function and Cr excretion are common [9], and agree with the recent analysis of the NHANES urine samples regarding the confounding variables using urinary Cr [5].

Although SG is less affected by muscle mass and energy intake than Cr, there are certain potential confounders with its use. The measured SG reflects the average SG of all major solutes present in the urine, with higher contribution for compounds with higher molecular weight. This implies that phosphates, sulfates, glucose, Cr, and proteins contribute more than chloride and urea [20]. SG has an important limitation in the setting of diabetes. Glucosuria or proteinuria affects SG measurement, and should be excluded from analysis. In a population study to evaluate the suitability of spot urine samples, Hinwood et al. [21] suggested that adjusting As measurements in spot urine samples may not be required. On the contrary, this study emphasizes the need to adjust urinary concentration for SG when measuring inorganic As.

Interest in the role of As in the development of diabetes is based on several animal models where toxic As levels led to the development of insulin resistance [3]. In epidemiologic studies, high chronic exposure to inorganic As in drinking water was associated with diabetes [22–25]. High chronic exposure to inorganic As in occupational settings was also related to higher levels of glycated hemoglobin [26]. However, the role of low-level As exposure to the development of diabetes is not yet settled. Navas-Acien et al. [4] suggested a positive association between total urinary As, likely reflecting inorganic As exposure from drinking water and food, with the prevalence of type 2 diabetes in a population with low-to-moderate As exposure. A second analysis of the same database that excluded organic As (AsB) [5] showed no evidence of increased risk in diabetic subjects. Our study is in agreement with studies indicating that low-level exposure to inorganic As may not be strongly correlated to glycemia or measures of insulin resistance.

A significant correlation between adjusted urinary spot or 24-hour As samples and HOMA-IR, waist circumference, or glycated hemoglobin was not found. However, by virtue of its small sample size and cross-sectional design, the study would have limited value in detecting a role for As in the development of insulin resistance and/or diabetes. Although differences in spot urinary As adjusted for Cr between diabetic and non-diabetic subjects were observed, this was likely due to the fact that urine Cr levels do not independently predict hydration status in the setting of diabetes. Moreover, while it is likely that the present study is underpowered to find a relation between low-level inorganic As exposure and diabetes, it should also be noted that correlations of this type do not necessarily reflect total As exposure or steady-state excretion of urinary As. Future studies are needed to estimate the effect of diabetes on steady-state excretion of As in urine.

Conclusions

The findings reported herein suggest that spot urinary As requires appropriate normalization. Although adjusting for urinary Cr apparently has a strong correlation to 24-hour measurement of urinary As, it might be inadequate when investigating diabetic patients. Alternatively, adjustment by SG may provide a superior approach because it is based on a physical rather than a metabolic property.

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Disclosure Statement

The authors have no conflict of interest to declare.

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