



Relationship Between Serum Levels of Arsenic, Cadmium, and Mercury and Body Mass Index and Fasting Plasma Glucose in a Mexican Adult Population

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Abstract

In Mexico, few studies have analyzed the associations between toxic elements and metabolic diseases. In the present study, we analyzed the associations between serum arsenic (As), cadmium (Cd), and mercury (Hg) levels and body mass index (BMI) and fasting plasma glucose (FPG) in a Mexican adult population. Anthropometric data corresponding to 86 Mexican healthy adults (59 females and 27 men) were analyzed. FPG was analyzed by an enzymatic colorimetric method, and serum As, Cd, and Hg levels were analyzed by inductively coupled plasma–mass spectrometry (ICP–MS). The data show that the median serum As, Cd, and Hg levels were relatively higher in females (As = 1.78 ng mL⁻¹, Cd = 1.00 ng mL⁻¹, Hg = 0.96 ng mL⁻¹) than those in males (As = 1.22 ng mL⁻¹, Cd = 0.91 ng mL⁻¹, Hg = 0.95 ng mL⁻¹). However, these differences were not statistically significant ($p \geq 0.097$). We also found that the median level of As significantly increased with an increase in the body weight categories (normal weight = 1.08; overweight = 1.50; obesity = 2.75; $p < 0.001$). In addition, a positive association between serum As levels and FPG before and after adjustment for BMI was demonstrated ($\text{Rho}_{\text{Unadjusted}} = 0.012$; ($\text{Rho}_{\text{Adjusted}} = 0.243$, $p = 0.032$). Serum As levels are positively associated with BMI and FPG in the adult population of Mexico. Nevertheless, these results need to be replicated and confirmed with a larger sample size.

Keywords Toxic elements (As · Hg · And Cd) · Serum · Body mass index · Glucose · Mexican adult population

Introduction

Body mass index (BMI) has been used to assess the body weight categories of an individual and can be classified into normal weight (NW), overweight (OW), and obesity (OB)

[1, 2]. Moreover, obesity is defined as an excessive accumulation of fat in the body and is often subdivided into three classes (1 (BMI of 30 to <35), 2 (BMI of 35 to <40), and 3 (BMI of 40 or higher)). Furthermore, the World Health Organization (WHO) report shows worrying data on the

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increase in OW and OB [3]; their prevalence has increased threefold since 1975. Today, the estimated number of individuals living with OW and OB exceeds 2 billion.

OW and OB are considered reversible diseases if they are controlled early enough. Nevertheless, OW and OB contribute to the development of other metabolic diseases that are not reversible, such as diabetes mellitus, metabolic syndrome, dyslipidemia, and cardiovascular diseases [4–8]. Recently, OW and OB have been associated with increased severity of disease and mortality in the adult population with COVID-19 disease [9–11].

According to the Mexican National Health and Nutrition Survey (2016), the prevalence of OW and OB in children and adults is higher in México than that in other countries with Latin American populations [12]. In addition, in 2017, the Organization for Economic Cooperation and Development (OECD) reported the prevalence of OW and OB worldwide, and Mexico had the highest prevalence of obesity in the population aged 15–74 years [13].

Today, human health risks are more evident by exposure to toxic elements, and billions of people worldwide have been exposed to arsenic (As), mercury (Hg), and cadmium (Cd) in very small amounts by the intake of food, water, and air. In addition, the WHO reported that these toxic elements, including lead (Pb), are among the top ten chemicals of public health concern [14]. Furthermore, recent evidence has shown that As, Hg, and Cd are associated with the development of metabolic diseases, especially diseases that have been associated with obesity [15–20]. The exact mechanisms of As, Hg, or Cd in the body are not completely understood; however, these chemicals have been associated with oxidative stress, inflammation, insulin resistance, and adipokine expression in humans [21–26]. Hg induces oxidative stress, inflammation, and insulin resistance, and it is associated with hypertension and dyslipidemia [25–27]. Cd is associated with endocrine disruption, and its mechanisms of toxicity include oxidative stress, inflammation, and interference with trace element metabolism of Zn, Cu, and Cr [23, 28]. Moreover, exposure to As has been associated with the pathophysiology of obesity and diabetes mellitus due to free radical formation, which contributes to inflammation and oxidative stress in these diseases [21, 22]. Fasting plasma glucose (FPG) is a test used for the diagnosis of diabetes [29]. FPG is a risk indicator for obesity, and in turn, it has been associated with diabetes mellitus [30] and metabolic syndrome [31]. Hg, As, and Cd exposure could alter glucose regulation.

In Mexico, few studies have been carried out to evaluate the association of toxic elements with metabolic diseases. For this reason, the present work evaluates the serum Cd, Hg, and As levels and their association with BMI, as an obesity marker, and FPG in a Mexican adult population.

Materials and Methods

Study Characteristics

In this cross-sectional study, we included a total of 86 Mexican adult students (59 females and 27 men, between 19 and 24 years old, with a median age of 20.3 years) with normal glucose tolerance (NGT) from the Faculty of Nursing and Nutrition of the University Autonomous of San Luis Potosí in San Luis Potosí, Mexico. Adults with FPG \leq 126 mg/dL were considered to have NGT according to the 2003 American Diabetes Association criteria [32]. By self-report, adults with diseases that could confound the association analysis in the study, such as AIDS and/or chronic liver/kidney disease and/or any cancer, were excluded from this study.

Ethical Approval

This work was conducted according to the ethical criteria from the Guidelines of the General Health Law on Health in Mexico and following the guidelines of the Declaration of Helsinki. The Ethics Committee of the Faculty of Nursing and Nutrition, Autonomous University of San Luis Potosí, approved the protocol with the register number 2014–092, and written consent forms were obtained from all participants.

Anthropometry

For the measurement of BMI, height and weight were determined with a portable stadiometer (Seca, Hamburg, Germany) and a bioelectrical impedance scale (SECA Model 818), respectively. BMI was calculated as the ratio of weight in kilograms and height squared in centimeters. The categories of body weight were classified into three categories: BMI $<$ 25 was NW, BMI \geq 25 was OW, and BMI \geq 30 was OB.

Collection and Preparation of Serum Samples

Serum samples were collected at the university's clinical analysis laboratory. Standardized protocols were used for serum extraction. This process is summarized in three steps. First, 5 mL of peripheral blood was extracted by venipuncture in a sterile vacutainer tube after 12 h of fasting. Second, serum was separated after blood coagulation by centrifugation at 4000 rpm at 4 °C for 10 min. Third, serum samples were collected with transfer pipettes and stored in Eppendorf tubes at -80 °C until analysis.

Samples were thawed overnight at 4 °C in a cold room. Then, 200 μL from each serum sample was transferred to a 1.5-mL Eppendorf tube. Iridium (Ir) and indium (In) were added to the samples at a concentration of 10 ng mL^{-1} as internal standards, and 10 ng mL^{-1} gold (Au) was added to avoid Hg losses during the treatment of the sample. In addition, 100 μL of concentrated high purity HNO_3 was added to each sample. Finally, the samples were homogenized and stored at room temperature.

Samples were recovered from Eppendorf tubes using micropipettes and 3 mL of concentrated HNO_3 . Samples were transferred into Teflon tubes for microwave digestion (MARS6 CEM, Matthews, North Carolina). Then, 5 mL concentrated HNO_3 was added to the Teflon tubes. The acid digestion process consisted of a temperature increase to 180 °C and a digestion time of 20 min. All samples were recovered from the Teflon tubes with concentrated HNO_3 . Then, they were dried on plates by evaporation using a glass beaker of 50 mL and watch glass to prevent mass losses from projections. Samples were diluted to 10 mL with 2% v/v HNO_3 concentrated for Hg, As, and Cd measurement by inductively coupled plasma–mass spectrometry (ICP–MS). The Eppendorf tubes, Teflon tubes, glass beaker, and volumetric flasks were previously decontaminated. Moreover, blank samples were prepared to quantify the contribution of As, Hg, and Cd using concentrated HNO_3 and water.

The concentrated HNO_3 used in all processes was of high purity and purified by a Milestone Duopur system (Milestone Srl, Italy). Moreover, water of high purity $> 18 \text{ M}\Omega \text{ cm}$ was obtained from a Milli-Q® system (Millipore, México) and used for the treatment samples and external curve preparation.

Quantification of Hg, Cd, and As by ICP–MS

Hg, Cd, and As were measured by ICP–MS (iCAP from Thermo Scientific, Germany) with collision reaction cells (helium mode) and kinetic energy discrimination (KED). For mass calibration, a certified reference material (CRM) was used for ICP–MS iCAP Q/RQ. Ba, Bi, Ce, Co, In, Li, and U at a concentration of $1.00 \pm 0.05 \mu\text{g L}^{-1}$ were used (Alfa Aesar, Specpure, USA). Quantification of Hg, Cd, and As was performed using CRMs at a concentration of $1000 \pm 0.06 \mu\text{g mL}^{-1}$ (High Purity Standards, USA). Concentrations used for the preparation of external calibration were 0.01, 0.05, 0.1, 0.5, 1, 5, 10, and 25 ng mL^{-1} . Moreover, Ir, In, and Au were obtained at a concentration of $1000 \pm 0.06 \mu\text{g mL}^{-1}$ from High Purity Standards, USA. Finally, serum Hg, Cd, and As concentration levels were calculated by subtracting reagent blanks and the recovery percentage of Ir and In. Figure 1 shows the calibration curve and linear regression of each element. In addition, quality

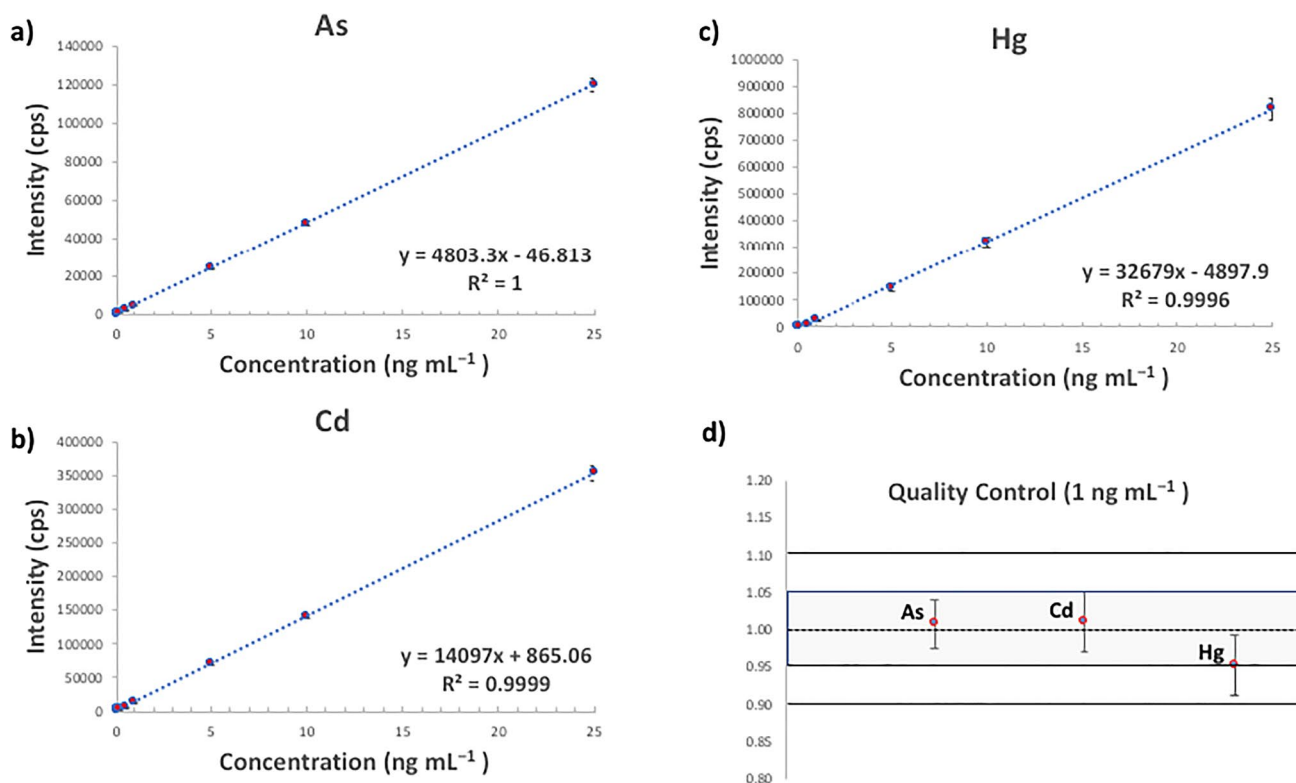


Fig. 1 Calibration curves and quality control; a) As, b) Cd, c) Hg, and d) quality control used in the analysis of serum sample ($n=7$)

control of 1 ng mL^{-1} showed standard deviations less than 5% for $n=7$. The reagent blank intensities of As, Cd, and Hg in terms of count per second (cps) were 15 ± 9 cps, 139 ± 49 cps, and 31 ± 15 cps, respectively. Moreover, the recovery yields of In and Ir were $89 \pm 5\%$ and $93 \pm 3\%$, respectively. For calculating the concentrations of As, Cd, and Hg, only Ir was used because this had better recovery in the treatment process.

Glucose Measurements

Glucose was measured with commercially available kits from Spinreact (Glucose LQ, LIQ423) and using a Halo DB-20 UV-Vis spectrophotometer from Dynamica (UK). All determinations of glucose were performed according to the manufacturer's protocol.

Statistical Analysis

The Shapiro-Wilk test was used to determine the normality of the distribution of variables. Chi-square tests were employed to compare frequencies between study groups. The variables that did not show rich normality were normalized with rank-based inverse normal transformation (Supplementary Table 1) [33]. According to the normality of the raw data of the quantitative variables (Supplementary Table 1), Student's t , Mann-Whitney U , and Kruskal-Wallis tests were used to compare these variables between the study groups. Additionally, Spearman's rho coefficient was determined (unadjusted model), and Spearman's rank correlation analysis (with the normalized data) adjusted for age and sex was performed to evaluate the associations between As, Cd, and Hg and BMI and FPG. The associations between As, Cd, and Hg and FPG were additionally adjusted for BMI. SPSS software (version 22.0, BMI, NY, USA) was used to perform the statistical analysis, and a two-sided p value < 0.05 was considered significant.

Results

General Characteristics of the Sample Study

The general characteristics of the sample study are shown in Table 1. The variables of age and BMI were homogenous between the female and male groups ($p \geq 0.152$). However, the mean FPG was significantly higher in males than that in females ($p = 0.026$). The median levels of serum As, Cd, and Hg were relatively higher in females than those in males (As = 31.46%, Cd = 9.0%, Hg = 1.04%). However, these differences were not statistically significant ($p \geq 0.097$). Moreover, the frequency of overweight and obesity was homogeneous in the female and male groups ($p = 0.726$).

Table 1 General characteristics of total sample

Trait	Female ($N = 59$)	Male ($N = 27$)	p value NA
Age (years)	20.0 (19.0–22.0)	20.0 (19.0–22.0)	0.555
BMI (kg/m^2)	27.1 (24.6–29.8)	26.2 (23.3–27.9)	0.152
FPG (mg/dL)	83.97 ± 5.64	87.30 ± 7.63	0.026*
As (ng/mL)	1.78 (1.10–2.84)	1.22 (0.40–2.47)	0.097
Cd (ng/mL)	1.00 (0.80–2.01)	0.91 (0.55–1.70)	0.282
Hg (ng/mL)	0.96 (0.93–1.03)	0.95 (0.93–1.00)	0.555
Overweight n (%)	29 (49.2)	14 (51.9)	0.726
Obesity n (%)	13 (22.0)	4 (14.8)	

Data are expressed as mean \pm standard deviation, median (interquartile rank), and N (%). Chi-square test was used to compare frequencies, and Student's t and U Mann-Whitney tests were used to continue variables. *Abbreviations*: NA, not analyzed; BMI, body mass index; FPG, fasting plasma glucose; As, arsenic; Cd, cadmium; Hg, mercury. *Significant p values ($p < 0.05$)

Concentration of Serum As, Cd, and Hg by Body Weight Categories

The results obtained for the concentrations of serum As, Cd, and Hg by body weight categories are shown in Table 2. The median level of As increased with an increase in the body weight categories ($p < 0.001$). However, the median levels of Cd and Hg did not show significant differences among the body weight categories analyzed ($p \geq 0.166$; Table 2). Figure 1 shows the calibration curve and linear regression of each element. In addition, quality control of 1 ng mL^{-1} showed standard deviations less than 5% for $n = 7$. The reagent blank intensities of As, Cd, and Hg in terms of count per second (cps) were 15 ± 9 cps, 139 ± 49 cps, and 31 ± 15 cps, respectively. Moreover, the recovery yields of In and Ir were $89 \pm 5\%$ and $93 \pm 3\%$, respectively. For calculating the concentrations of As, Cd, and Hg, only Ir was used because Ir had better recovery in the treatment process.

Associations Between Serum As, Cd, and Hg Levels and BMI and FPG

Table 3 shows the associations between serum As, Cd, and Hg levels and BMI and FPG before and after adjustment for age and sex. The results showed that the serum level of As was significantly associated with an increase in BMI and FPG level before and after adjustment for age and sex (BMI: $p_{\text{Unadjusted}} < 0.001$, $p_{\text{Age and sex adjusted}} < 0.001$; FPG: $p_{\text{Unadjusted}} = 0.030$; $p_{\text{Age and sex adjusted}} = 0.012$; Table 3). We then analyzed the association between serum As level and FPG additionally adjusted for BMI, and the effect was still significant (Rho = 0.243, $p = 0.032$).

Table 2 Description of serum As, Cd, and Hg levels by nutritional categories

Trait	Normal weight (N = 26)	Overweight (N = 43)	Obesity (N = 17)	p value NA
As (ng mL ⁻¹)	1.08 (0.33–1.88)	1.50 (1.01–3.18)	2.75 (2.06–3.55)	< 0.001*
Cd (ng mL ⁻¹)	0.78 (0.30–1.95)	1.06 (0.84–1.65)	0.94 (0.75–2.39)	0.166
Hg (ng mL ⁻¹)	0.97 (0.93–1.02)	0.96 (0.93–1.04)	0.95 (0.92–1.01)	0.803

Data are expressed medians (interquartile rank). The Kruskal–Wallis test was used to compare continuous variables. *Significant *p* values (*p* < 0.05). Abbreviations: As, arsenic; Cd, cadmium; Hg, mercury

Table 3 Association of serum As, Cd, and Hg levels with BMI and FPG

Element	Trait	Unadjusted#	Adjusted for age and sex##
As (ng mL ⁻¹)	BMI	0.489 (< 0.001)*	0.446 (< 0.001)*
	FPG	0.237 (0.030)*	0.282 (0.012)*
Cd (ng mL ⁻¹)	BMI	0.180 (0.105)	0.119 (0.296)
	FPG	0.079 (0.480)	0.031 (0.789)
Hg (ng mL ⁻¹)	BMI	-0.032 (0.771)	0.091 (0.428)
	FPG	0.185 (0.087)	0.154 (0.176)

Data are expressed Spearman's rank correlation coefficient (*p* value). #Unadjusted Spearman's correlations; ##Spearman's rank correlation analysis adjusted for age, and age and sex. *Significant *p* values (*p* < 0.05). Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; As, arsenic; Cd, cadmium; Hg, mercury

Discussion

The results from this study allowed us to determine the associations between serum As, Cd, and Hg levels and BMI and FPG in a Mexican adult population. The analyses showed that Cd and Hg did not show any significant associations with these parameters, which is in contrast with other studies that reported associations between Hg or Cd and obesity [34–39]. The lack of association between Hg and BMI and FPG could be explained by the use of serum because whole blood has been considered a better biological sample to evaluate Hg exposure [40]. However, whole blood has been considered a complex sample in comparison with serum. Moreover, exposure to As, Cd, and Hg has been reported to be associated with obesity and diabetes mellitus, where they affect glucose homeostasis [34]. While we did not find a significant association between Cd and Hg and BMI and FPG, previous studies have reported that Cd and Hg exposure increases insulin resistance as a consequence of adiponectin secretion and disrupts pancreatic β -cells and insulin deactivation [41, 42].

Exposure to As has been attributed to food intake, where its main exposure occurs through drinking water that has high levels of As [43]. It is worth mentioning that As is not considered an obesogenic element. Nevertheless, the results obtained in this study show the existence of a

positive association between serum As levels and BMI and FPG. These results are consistent with other previously reported studies on the associations between As and obesity, glucose homeostasis, and diabetes mellitus [15]. Most of these previous studies propose a mechanism that acts through pancreatic oxidative damage, which impairs insulin synthesis and secretion by damaging pancreatic beta-cell functions. Additionally, insulin resistance in skeletal muscle increases gluconeogenesis in the liver and modulates other hepatic insulin signaling pathways [44–47]. However, to date, the full mechanism to explain the associations between As and obesity and diabetes mellitus has been unclear. Animal experimental models have shown that As exposure significantly increased reactive oxygen species and malondialdehyde formation in pancreatic β -cells, leading to decreased insulin secretion [16]. Other studies have shown that PPAR γ –mTOR complex 2 (mTORC2) signaling is activated at low concentrations and induces insulin resistance [48]. Thus, it is clear that As plays a significant role in the development of obesity and diabetes mellitus. Nevertheless, future studies are necessary to evaluate the associations between As exposure and genetic factors. Moreover, some variants in specific genes could represent a risk of developing impaired metabolic pathways that could exacerbate the metabolic effects of any toxic element exposure [49, 50].

It is generally recognized that a sedentary lifestyle with high caloric food intake is crucial in the development of obesity and related metabolic complications. Nevertheless, our results show for the first time a significant association between serum As levels and BMI and FPG in a Mexican population, which is relevant due to a lack of epidemiological studies in this country. Thus, it is important to replicate our results and perform more epidemiologic and genetics studies to accumulate enough evidence to contribute to understanding the relationship between As and obesity and markers of glucose metabolism in the Mexican population.

One limitation of this study is the small sample size that was analyzed. Additionally, we recognize that the inclusion of data regarding demographic characteristics of the population and food and water intake could increase the relevance of our results. Moreover, in the case of exposure to Hg and Cd, it is important to consider smoking habits [51] and fish

and shellfish intake because they contain elevated levels of methylmercury in their tissues [52]. Finally, our study did not include body fat percentage in the analysis, which could improve the analysis of the associations between As, Cd, and Hg levels and body fat.

Conclusion

This study reveals a significant positive association between serum As levels and BMI and FPG in a Mexican adult population. Nevertheless, a significant association between serum Cd and Hg levels and BMI or FPG was not demonstrated. The epidemiologic and genetic studies related to toxic elements and metabolic diseases could strengthen our evidence.

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Availability of Data and Material The dataset of this study is available from the corresponding authors on reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

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