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Association of urinary metal levels with human semen quality: A cross-sectional study in China

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ABSTRACT

Background: Exposure to metals, including essential and nonessential elements, has been linked to male reproductive health in animals. However, findings from human studies are inconsistent.
Objective: To examine the associations between metal exposure at environmental levels and semen quality in a Chinese population by performing repeated measurements of urinary metals to estimate individual-level exposure.
Methods: From March to June 2013, 1052 men seeking semen evaluation were recruited from the Reproductive Center of Tongji Hospital in Wuhan, China. Each man provided one semen sample and two urine sample. *Semen* quality parameters and urinary levels of 18 metals were determined. Associations between the urinary metal levels and semen quality parameters were assessed using confounder adjusted linear and logistic regressions. Restricted cubic spline analysis was performed to assess dose-response relationships between continuous metal measurements and outcomes.
Results: Urinary levels of cadmium were significantly inversely associated with progressive sperm motility and total motility (both $P < 0.02$) based on multivariable linear regression models, consistent with the trends of increased odds ratios for below-reference semen quality parameters observed in the logistic models (both $P < 0.05$). Additionally, we found significant inverse associations of urinary molybdenum and lead with percentages of normal sperm morphology (both $P < 0.05$). These associations remained suggestive or significant after adjustment for multiple testing. They were also robust to the simultaneous consideration of multiple metals, and curves of restricted cubic spline showed clear dose-response relationships.
Conclusion: Our findings suggest that environmental exposure to cadmium, molybdenum and lead may contribute to a decline in human semen quality.

1. Introduction

Heavy metal pollution in China has become a serious problem due to rapid industrialization and urbanization throughout the last two decades (Qu et al., 2012), and exposures encountered in the environment have become an increasing concern due to the potential human health risks, including effects on reproductive health. Toxic elements, such as aluminum, arsenic, cadmium, lead, antimony, thallium and uranium, are nonessential xenobiotics and have been found to cause reproductive toxicity in rats (Gregotti et al., 1992; Llobet et al., 1991; 1995; Oliveira et al., 2009; Omura et al., 2002; Pant et al., 2001). Essential elements, such as chromium, manganese, iron, cobalt, nickel, copper, zinc, selenium, molybdenum and tin are necessary for good health, but they have also been linked to impaired semen quality if above specific levels in animals (Babaei and Abshenas, 2013; Chandra et al., 2007; Das and Dasgupta, 2000; Lyubimov et al., 2004; Pedigo et al., 1988; Wellejus et al., 2000).

In humans, a number of studies have determined the associations between non-occupational exposure to metals and semen quality (Benoff et al., 2009; Meeker et al., 2008; Mendiola et al., 2011; Telisman et al., 2007; Zeng et al., 2015). However, the data regarding

Abbreviations: Al, aluminum; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; FDR, the false discovery rate; Fe, iron; ICC, intraclass correlation coefficient; Mn, manganese; Mo, molybdenum; Ni, nickel; Pb, lead; Sb, antimony; Se, selenium; Sn, tin; Tl, thallium; U, uranium; W, tungsten; Zn, zinc.

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some metals have been limited (e.g., chromium, iron, manganese, cobalt, copper, arsenic), lacking (e.g., aluminum, tin, antimony, thallium and uranium), or inconsistent across studies (e.g., nickel, molybdenum, cadmium and lead). Previously published studies have used measurements of metals in single urine or blood samples as biomarkers to estimate individual-level exposure. Because most metals in human biological samples can vary greatly over time due to variable exposures driven by changes in diet, lifestyle or the daily activities of a person (e.g., cobalt, nickel, copper, arsenic, molybdenum, lead) (Smolders et al., 2014; Wang et al., 2015a), using a single measurement to represent an individual's average exposure over time can result in misclassifications of exposures that potentially bias the risk estimates. Additionally, the limited sample sizes in previous studies may have been insufficient to produce precise results. Consequently, the effect of environmental exposure to metals on semen quality in humans remains uncertain.

Measurements of metals in urine are often used as biomarkers in human investigations, especially in surveys involving a large number of participants, because the collection of samples is relatively simple and non-invasive (Health Canada, 2010; CDC, 2014). Our recent study of metal variability in 529 urine samples from 11 healthy adult Chinese males has suggested that the collection of multiple urine samples from each study participant improved the classification of an individual's 3-month average exposure (Wang et al., 2015a). Therefore, we conducted a large-scale study to investigate the association between semen quality and 18 urinary metals (aluminum, chromium, manganese, iron, cobalt, nickel, copper, zinc, arsenic, selenium, molybdenum, cadmium, tin, antimony, tungsten, thallium, lead and uranium) in a Chinese population by performing repeated measurements of metals for each study participant.

2. Materials and methods

2.1. Population and data collection

Our study was approved by the Ethics Committee of the Tongji Medical College. The study participants were male partners in couples who participated in a hospital-based cross-sectional study of exposure to environmental contaminants and male reproductive health, as described in our previous study (Wang et al., 2015b). Briefly, from March to June 2013, a total of 1490 men were invited to participate in the study, of which 1247 (83.69%) ultimately enrolled. After a self-reported abstinence period of 2–7 days, each participant was asked to provide two spot urine samples and a semen sample, as well as to complete a questionnaire on the day of their clinic visit. The information collected included demographic characteristics, lifestyle habits, occupational exposure, medical history and history of having ever fathered a pregnancy. After excluding volunteers with self-reported health conditions (e.g., epididymitis, vasectomy, varicocele, orchiditis, vesiculitis, hernia repair complicated by testicular atrophy, testis injury, undescended testicle, diabetes or adrenal disorder) that may affect male reproductive health and occupational exposure to metals, 1052 participants remained in the current analysis. Each participant signed written informed consent before participation.

2.2. Urine collection and metal analysis

A single spot urine sample was collected from each participant on the day of his clinic visit. Given the considerably high intra-day and relatively low inter-day variability of metal concentrations in spot urine samples (Wang et al., 2015a), a second spot urine sample was collected

Table 1
Demographic categories [n (%) or mean ± SD] according to semen parameters[a].

Category	All subjects[d], n = 1052	Comparison subjects[e], n = 661	Semen quality parameter			
			Progressive motility <32%, n = 292	Total motility <40%, n = 338	Concentration <15 × 10^6/mL, n = 98	Total count <39 × 10^6, n = 128
Age, years	32.06 ± 5.36	31.95 ± 5.34	32.21 ± 5.20	32.38 ± 5.45	31.61 ± 5.18	32.17 ± 5.25
BMI, kg/m^2	23.28 ± 3.15	23.29 ± 3.22	23.27 ± 3.10	23.21 ± 3.06	22.99 ± 3.05	23.53 ± 3.00
Daily cigarette consumption	7.25 ± 8.38	7.41 ± 8.51	6.60 ± 7.47	7.02 ± 8.34	7.10 ± 7.13	7.08 ± 8.99
Ever fathered a pregnancy[b]						
Yes	422 (40.34)	280 (42.55)	108 (37.24)	126 (37.58)	29 (30.11)	41 (32.79)
No	624 (59.66)	378 (57.45)	182 (62.76)	210 (62.42)	69 (69.89)	85 (67.21)
Race						
Han	1025 (97.43)	641 (96.97)	286 (95.95)	332 (98.18)	97 (98.92)	126 (98.36)
Other	27 (2.57)	20 (3.03)	6 (2.05)	6 (1.82)	1 (1.08)	2 (1.64)
Abstinence time[c], days						
<3	121 (11.51)	72 (10.91)	32 (10.96)	37 (10.94)	12 (11.83)	26 (20.16)
3–5	679 (64.61)	441 (66.82)	176 (60.27)	209 (61.40)	65 (66.67)	80 (62.10)
>5	251 (23.88)	147 (22.27)	84 (28.77)	92 (27.66)	21 (21.50)	22 (17.74)
Education level						
Less than high school	397 (38.06)	253 (38.57)	109 (37.72)	127 (37.23)	42 (42.86)	48 (37.40)
High school and above	646 (61.94)	403 (61.43)	180 (62.28)	207 (62.77)	54 (57.14)	79 (62.60)
Smoking status						
Never-smoker	411 (39.07)	248 (37.51)	124 (42.47)	145 (42.55)	41 (41.93)	52 (41.13)
Ever-smoker	641 (60.93)	413 (62.49)	168 (57.53)	193 (57.45)	57 (58.07)	76 (58.87)
Former	119 (11.31)	75 (11.35)	34 (11.64)	37 (10.33)	13 (11.83)	13 (9.68)
Current	522 (49.62)	338 (51.14)	134 (45.89)	156 (47.12)	44 (46.24)	63 (49.19)
Alcohol use						
Yes	411 (39.07)	244 (36.91)	129 (44.64)	144 (42.86)	43 (44.09)	56 (44.36)
No	641 (60.93)	417 (63.09)	163 (55.36)	194 (57.14)	55 (55.91)	72 (55.64)
Income, RMB yuan/month						
≤3000	462 (44.00)	279 (42.34)	129 (44.18)	152 (44.07)	49 (47.31)	65 (50.0)
3000–6000	401 (37.83)	248 (37.63)	116 (39.73)	137 (41.03)	37 (39.79)	45 (35.48)
≥6000	187 (18.17)	132 (20.03)	47 (16.09)	49 (14.90)	12 (12.90)	18 (14.52)

[a] The between-group differences in population demographic data stratified by semen quality reference values were analyzed using Chi-square tests for categorical variables and independent sample t-test for continuous variables.
[b] The variable differed significantly between the comparison and below-reference groups for sperm concentration and total count ($P < 0.05$).
[c] The variable differed significantly between the comparison and below-reference group for total count ($P < 0.05$).
[d] A total of 2 patients had missing information on age, 6 on the history of a successful pregnancy, 9 on education level, 1 on abstinence time and 2 on income.
[e] The comparison group consists of men with all four semen parameters greater than the reference level.