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Burden of cadmium in early childhood: Longitudinal assessment of urinary cadmium in rural Bangladesh

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ABSTRACT

Chronic cadmium exposure is associated with many adverse health effects in adults, but little is known about the scenario early in life. This study assessed cadmium exposure and body burden in young children, born to women with known cadmium exposure via rice. As part of our ongoing population-based, longitudinal study of health effects of early-life toxicants exposure in rural Bangladesh, we measured cadmium in urine of about 350 children at 1.5 and 5 years of age, and in 92 children at 3 months of age. Median cadmium concentrations in urine were 0.30, 0.16 and 0.30 μg/L at 3 months, 1.5 and 5 years of age, respectively (0.6 μg/L in mothers). Cadmium concentrations in infant's urine correlated with concentrations in maternal breast milk, saliva, and urine. As expected, concentrations in urine increased from 1.5 to 5 years of age. Rice (median 47 μg Cd/kg) is most likely the main source of exposure. In conclusion, we found unexpectedly high cadmium exposure among children in rural Bangladesh. Urinary cadmium concentrations were particularly elevated at 3 months of age, indicating limited reabsorption and accumulation of cadmium in the kidneys, known to be the main site of cadmium burden in older children and adults.

1. Introduction

The main source of exposure to the toxic and carcinogenic metal cadmium is basic foods like cereals and vegetables (EFSA, 2009), which means that the exposure is life-long. Chronic exposure even to fairly low cadmium doses has repeatedly been shown to cause a wide range of health problems in adults, including toxic effects in kidneys, bone, endocrine effects, and cancer (Järup and Åkesson, 2009; Satarug et al., 2010), but studies involving children are limited (Schoeters et al., 2006). Experimental animal studies have indicated developmental toxicity of cadmium, although this was not confirmed in humans (Cao et al., 2009). Urinary cadmium concentrations in 5–14-year-old children have been associated with immunosuppression (Ritz et al., 1998), and experimental studies indicated increased susceptibility to immunotoxicity during early development (Pillet et al., 2005). The toxicity of cadmium, which occurs in biological tissues in oxidation state 2+, is largely related to the high affinity for sulfhydryl groups and thiolate anions, which also is influencing the toxicokinetics (Zalups and Ahmad, 2003). Binding to metallothionein is a key feature in cadmium kinetics and toxicity (Klaassen et al., 2009).

Although prenatal exposure to cadmium usually is low, as cadmium accumulates in the placenta (Osman et al., 2000), the cadmium concentration in umbilical cord blood increases with increasing maternal exposure (Kippler et al., 2010). Negative associations have been found between maternal cadmium exposure and size at birth (Kippler et al., 2010; Llanos and Ronco, 2009; Salpietro et al., 2002; Zhang et al., 2004) as well as pre-term delivery (Kippler et al., 2010; Nishijo et al., 2002). Part of these effects may, however, be related to accumulation of cadmium in placenta with resulting impairment of essential trace elements like zinc to the fetus (Kippler et al., 2010). Another important finding is the observed estrogenic effects of cadmium in female mice exposed prenatally (Johnson et al., 2003). Also the concentration of cadmium in breast milk is generally low, although it increases with increasing maternal exposure (Kippler et al., 2009b). On the other hand, elevated concentrations of cadmium in infant food may cause much higher exposure. It has been calculated that toddlers (0.5–6 years of age) have twice as high intake of cadmium from food (3.3 μg/kg b.w. per week) as adults (EFSA, 2009). Experimental studies indicate higher intestinal absorption of cadmium in infancy than later in life (Eklund et al., 2003), however, human data are lacking.

We have recently showed that women in rural Bangladesh have elevated cadmium exposure, probably mainly from the rice-based

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Table 1
Characteristics and measured variables, including cadmium concentrations in urine, of the studied mothers and their children at 1.5 and 5 years of age.

Characteristic (unit)	*n*	Mean	Median	10–90 percentile
Maternal				
Age (years)	443	27	26	19–34
Height (cm)	444	150	150	144–157
Weight (kg)	444	45	44	37–54
Body mass index (kg/m^2)	442	19.9	19.5	16.9–24
Parity (no. of children)	442	1.4	1.0	0–3.0
Urinary cadmium (μg/L)	444	0.77	0.55	0.21–1.5
1.5-Year-old children				
Age (months)	345	18.0	18.0	17.9–18.2
Waz	319	−1.69	−1.69	−2.9 to 0.43
Haz	319	−1.98	−1.97	−3.5 to 0.69
Gestational week at birth	345	39	39	37–41
Birth weight (g)	330	2693	2691	2155–3240
Birth length (cm)	329	47.9	48.0	45.0–50.4
Urinary cadmium (μg/L)	347	0.26	0.16	0.08–0.46
Boys	178	0.25	0.15	0.08–0.41
Girls	167	0.28	0.18	0.08–0.56
5-Year-old children				
Age (years)	320	5.3	5.2	5.2–5.4
Waz	320	−1.89	−1.90	−3.1 to 0.84
Haz	320	−1.63	−1.61	−2.8 to 0.35
Urinary cadmium (μg/L)	332	0.37	0.31	0.18–0.58
Boys	154	0.39	0.31	0.19–0.59
Girls	152	0.35	0.29	0.17–0.58

diet (Kippler et al., 2007, 2009a). The aim of the present study was to assess the exposure and accumulation of cadmium in infants and young children born to the studied women. Undernutrition, which we found increased the cadmium uptake in the mothers, mainly through binding of Cd^{2+} to the divalent metal transporter DMT1, is prevalent in this population (Kippler et al., 2009a), and an additional aim is to evaluate the impact of nutrition on the cadmium burden in the children.

2. Materials and methods

2.1. Study area and study population

Our ongoing research on health effects of early-life exposure to arsenic, cadmium and other toxic agents is nested into a population-based food and micronutrients supplementation trial in pregnancy (Maternal and Infant Nutrition Interventions of Matlab; MINIMat), conducted in Matlab, located approximately 53 km south-east of Dhaka. About 4500 women in early pregnancy were recruited from November 2001 to October 2003 (Tofail et al., 2008). In Matlab, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has a Health and Demographic Surveillance System (HDSS), which is updated regularly with information collected by community health workers who visit every household on a monthly basis recording all vital events. Mothers were followed up from early gestation to 6 months postpartum, and their children have so far been followed up at 1.5 (Hamadani et al., 2010) and 5 years of age (Gardner et al., manuscript), at which times urine samples were collected. Of the 2119 women recruited from January 2002 to December 2002, 500 were randomly selected for evaluation of exposure to cadmium and associated health effects in their children. In total, 347 of those 500 women were followed up at 6 months postpartum and reasons for loss to follow-up have been discussed previously (Kippler et al., 2009b). In the present study we have measured concentrations of cadmium in urine of the mothers and their children at 1.5 and 5 years of age. Cadmium in urine is a recognized biomarker of chronic cadmium exposure and related to cadmium accumulation in the kidneys, the main storage site of cadmium with a half-time of 10–30 years (Järup and Åkesson, 2009).

In a sub-sample of the children we also measured urinary cadmium in infancy. We used residual urine samples of 3 months old infants participating in a validation of questionnaire data on infant feeding behavior, where intake of breast milk and non-breast milk water were measured in 98 mother–infant pairs, using the dose-given-to-the-mother deuterium dilution technique (Moore et al., 2007). We analyzed cadmium in urine of the infants and their mothers, as well as in breast milk, collected from their mothers at 2 months postpartum. Two infant urine samples and one saliva sample did not contain enough volume to enable cadmium measurements, so total numbers of available samples were 96 and 97, respectively. Urine was available for 92 of the mothers and breast milk for 79.

Trained research assistants recorded children's weight using electronic scales (accurate to 100 g), and height using locally-made length boards. Age- and sex-standardized *Z*-scores (weight-for-age, WAZ; height-for-age, HAZ; BMI-for-age, BAZ) were calculated (Gardner et al., manuscript; Hamadani et al., 2010). Extensive socio-economic (SES) data for all households, defined in terms of assets relevant for this rural area, were obtained from the HDSS database. Data on infant feeding practices were collected by questionnaires on a monthly basis (Moore et al., 2007). The study was approved by the Research Review Committee and Ethical Review Committee at ICDDR,B, as well as the Regional Ethics Committee at Karolinska Institutet, Sweden. Oral and written consent was obtained from the women.

2.2. Sample collection

At 3 months of age, urine was collected on cotton-wool placed in the infants' diapers (Moore et al., 2007). We tested for potential contamination of the urine by the cotton-wool (1.5 g) and found 0.034 ± 0.009 μg/L extracted by 10 mL of water or urine, which correspond to about 10% of the measured concentrations in infant urine. At 1.5 years of age, the urine was collected in plastic bags (tested free from cadmium) placed in potties, as previously described (Fangström et al., 2009). At 5 years of age, the urine was collected directly into plastic cups (Gardner et al., manuscript), in the same way as used by the mothers (Kippler et al., 2007). All urine samples were stored in acid-washed containers at −70 °C, and the samples were kept frozen during transport to Karolinska Institutet for further analysis.

In order to estimate the cadmium exposure from complementary diets, which often is based on rice (Faruque et al., 2008; Kimmons et al., 2005) we measured the cadmium content in uncooked rice samples collected from 63 of the participating families, though not concurrently with any of the urine samples.

2.3. Analysis of cadmium in biological samples

Measurements of cadmium *m*/*z* 111 in urine, saliva, breast milk and rice were performed with inductively coupled plasma mass spectrometry (ICPMS; Agilent 7500ce, Agilent Technologies, Waldbronn, Germany) with a collision/reaction cell system (Kippler et al., 2009a,b). Prior to the ICPMS analysis, breast milk and rice samples were acid digested with 65% nitric acid (Suprapur, Merck, Darmstadt, Germany) using a Milestone ultraCLAVE II microwave-assisted high-pressure digestion system (EMLS, Leutkirch, Germany). The limit of detection (LOD) for cadmium (three times the standard deviation (SD) of blank values) was <0.05 μg/kg for breast milk, 0.02 μg/kg for rice and <0.02 μg/L for urine and saliva. For quality control purposes we analyzed commercial reference materials (Seronorm^{TM} Trace Elements Whole Blood L-1, REF 201505; LOT MR4206, Seronorm^{TM} Trace Elements Whole Blood L-2, REF 201605; LOT 0503109, and Seronorm^{TM} Trace Elements Urine, REF 201205; LOT NO2525, SERO AS, Billingstad, Norway), which in general showed good agreement with recommend values (Kippler et al., 2009a,b). The certified reference material IRMM 804 rice flour (Institute for Reference Materials and Measurements, Belgium) was included in the analysis and there was a good agreement between the obtained value (mean ± SD 1.59 ± 0.02 μg/kg; *n* = 5) and certified reference value (1.61 ± 0.07 μg/kg).