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Renal and blood pressure effects from environmental cadmium exposure in Thai children

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ABSTRACT

Very few studies have shown renal and blood pressure effects from environmental cadmium exposure in children. This population study examined associations between urinary cadmium excretion, a good biomarker of long-term cadmium exposure, and renal dysfunctions and blood pressure in environmentally exposed Thai children. Renal functions including urinary excretion of β_2-microglobulin, calcium (early renal effects), and total protein (late renal effect), and blood pressure were measured in 594 primary school children. Of the children studied, 19.0% had urinary cadmium ≥ 1 μg/g creatinine. The prevalence of urinary cadmium ≥ 1 μg/g creatinine was significantly higher in girls and in those consuming rice grown in cadmium-contaminated areas. The geometric mean levels of urinary β_2-microglobulin, calcium, and total protein significantly increased with increasing tertiles of urinary cadmium. The analysis did not show increased blood pressure with increasing tertiles of urinary cadmium. After adjusting for age, sex, and blood lead levels, the analysis showed significant positive associations between urinary cadmium and urinary β_2-microglobulin and urinary calcium, but not urinary total protein nor blood pressure. Our findings provide evidence that environmental cadmium exposure can affect renal functions in children. A follow-up study is essential to assess the clinical significance and progress of renal effects in these children.

Introduction

Cadmium is an important environmental pollutant of public health concern due to its toxic effects to many organs (Aoshima, 2012; ATSDR, 2012; Bernard, 2008; IPCS, 1992; Järup and Akesson, 2009; Satarug et al., 2010). The principal environmental sources of cadmium exposure for the general population are food and tobacco smoking. Crops grown in cadmium-contaminated soil can contain elevated cadmium levels (ATSDR, 2012; IPCS, 1992). Prolonged excessive oral exposure can cause chronic cadmium poisoning (Aoshima, 2012; ATSDR, 2012; Bernard, 2008; IPCS, 1992; Järup and Akesson, 2009; Satarug et al., 2010). Urinary excretion of cadmium is a good biomarker of long-term cadmium exposure and body burden. The kidney is considered the critical target organ for chronic exposure to cadmium. Many studies in adults have shown that an initial sign of cadmium-induced nephrotoxicity is tubular proteinuria, usually demonstrated by increased urinary excretion of low molecular weight proteins such as β_2-microglobulin (β_2-MG), enzymes such as N-acetyl-β-D-glucosaminidase, and calcium (Aoshima, 2012; ATSDR, 2012; Bernard, 2008; IPCS, 1992; Järup and Akesson, 2009; Satarug et al., 2010). In persons with prolonged exposure to cadmium, tubular dysfunction may progress to glomerular impairment with increased urinary excretion of high molecular weight proteins. Although renal dysfunctions are well-known toxic effects of chronic cadmium exposure in adults, very few studies have shown these health effects in children. Children exposed to cadmium even at low exposure levels may have adverse effects since they may be more susceptible to toxicity than adults (ATSDR, 2012).

Cadmium is a widely but sparsely distributed element found in the earth's crust, primarily in association with zinc ores (Morrow, 2010). In the Mae Sot District, Tak Province, northwestern Thailand, paddy fields were irrigated from two creeks, which passed through an area where a zinc mine had been actively operated for >30 years. The zinc ores from the mine were carried to the smelting plant located 100 km from this area. About 69.2% of 91 sediment samples from the creeks and 85.0% of 1090 paddy soil samples contained cadmium content above the maximum

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permissible level of 3.0 mg/kg during the surveys in 2001–2004 (National Research for Environmental and Hazardous Waste Management, 2005; Pollution Control Department, 2004). Cadmium concentrations were low in the samples collected from the creeks before reaching the zinc area, became much higher when passing through this area, and then reduced with distance. Crops, including rice, grown in the areas were also found to contain markedly elevated cadmium levels during the surveys in 2001–2004. The cadmium-contaminated areas were discovered in the 12 rural villages of the district. Concentrations of other toxic substances such as inorganic arsenic, mercury, and lead in drinking and non-drinking water in the areas were lower than the WHO guideline values (Department of Environmental Health, 2013; WHO, 2011). The majority of residents were farmers and most of them consumed rice and other crops grown locally in the areas. Dietary cadmium and tobacco smoking were the two main routes of excessive cadmium exposure in adult residents living in these contaminated areas (Swaddiwudhipong et al., 2007, 2010b). Although the government prohibited food crop production in contaminated areas, some residents continued to grow rice for their own consumption. Our previous studies among adult residents in these contaminated areas showed high prevalence of renal dysfunctions, bone density loss in the elderly, hypertension, and urinary stone diseases (Limpatanachote et al., 2009, 2010; Nambunmee et al., 2010; Swaddiwudhipong et al., 2010a,c, 2011, 2012). The aim of this study was to determine cadmium effects on renal functions and blood pressure in environmentally exposed Thai children.

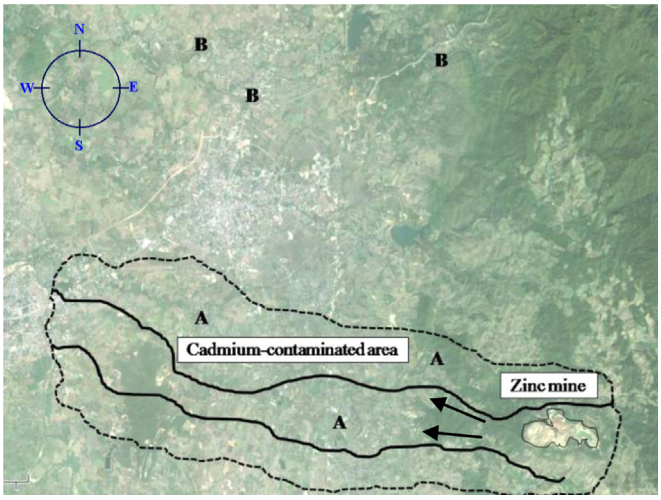

Fig. 1. Location of primary schools surveyed in and outside cadmium-contaminated areas.

Materials and methods

The study subjects

The study was conducted in 2013 among all children of the 3 primary schools randomly selected from 10 schools in the cadmium-contaminated villages and 3 schools outside the contaminated villages (comparison) with similar socio-demographic characteristics (28–40 km from the contaminated areas) (Fig. 1). Children with diagnosis of nephrotic syndrome and acute glomerulonephritis were excluded from the study. The study protocol was approved by the Mae Sot Hospital Ethical Committee and informed consent was obtained from the children's parents before the examination. Information from each participant included age, sex, medical history of renal diseases, tobacco smoking in the family members (exposure to passive smoking in children), and consumption of rice grown in cadmium-contaminated or other areas. Each participant was screened for urinary cadmium, renal functions, blood pressure, blood cadmium and lead. Study renal functions included urinary excretion of β_2-MG, calcium (early renal effects), and urinary total protein (late renal effect). Blood pressure was measured twice on the right arm in a sitting position and the average was recorded.

Laboratory analysis

Venous whole blood was collected for measurements of blood cadmium and lead. Thorough cleansing of the puncture site before blood collection and use of metal leakage-free sample collection equipment and containers were performed to prevent external contamination of samples. The blood cadmium and lead levels were determined by a graphite furnace atomic absorption spectrometry (AAS) (Varian Model AA280Z, Palo Alto, CA, USA) by the national laboratory, Thailand Ministry of Public Health. Quality assurance was conducted with simultaneous analysis of samples of the reference whole blood Lyphocheck® (Bio-Rad, Gladesville, New South Wales, Australia). The laboratory complied with mandatory quality control measures. The limits of detection (LOD) of our method were 0.05 μg/l for cadmium measurement and 0.1 μg/l for lead measurement. Concentrations of cadmium and lead in samples below the LOD were assigned the LOD divided by the square root of 2.

A spot morning urine sample was obtained from each child. Two 3 ml aliquots from each urine sample were for analysis of cadmium and β_2-MG. One drop of 0.5 N sodium hydroxide was added to one of the two aliquots showing the pH of 5 or below to adjust the urine pH of 6–8 for prevention of further degradation of β_2-MG in an acid condition. The remaining urine samples were for microscopic and biochemistry measurements. Urinary cadmium content was determined by an AAS. Quality assurance was conducted with simultaneous analysis of samples of the reference urine Lyphocheck® (Bio-Rad, Gladesville, New South Wales, Australia). Urinary β_2-MG concentration was determined by the enzyme-linked fluorescent assay (bioMérieux, Marcy-l'Étoile, France). Urinary calcium and total protein concentrations were measured by the colorimetric method (Bauer, 1981). Urinary creatinine concentration by the Jaffe reaction method (Butler, 1975) was used to adjust for urinary excretion of cadmium and the study markers. The samples were measured by using an auto-analyzer (Konelab 30, Thermo Electron Corporation, Vantaa, Finland). Quality assurance was conducted with simultaneous analysis of samples of the reference urine uTrol® and uTrol High® (Thermo Fisher Scientific Oy, Vantaa, Finland). Children with urinary creatinine <30 mg/dl during the survey had repeat urine sample collection and analysis in order to reduce the imprecise and unreliable results from highly dilute urine.

Children who had history of hematuria and/or a urinary stone or were found to express hematuria by urinary microscopic analysis during the survey were screened for the presence of a urinary stone by plain X-ray and ultrasonography. Prevalence of urinary