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Association of Elevated Urinary Cadmium with Urinary Stone, Hypercalciuria and Renal Tubular Dysfunction in the Population of Cadmium-Contaminated Area

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Abstract Excessive urinary calcium is the major risk of renal tubular dysfunction and urinary stone formation. We examined the association of elevated urinary cadmium with urinary stones and chronic kidney disease (CKD) in 1,085 study residents of 13 cadmium-contaminated villages. Elevated urinary cadmium was significantly correlated with urinary stone and CKD. Elevated urinary cadmium appeared to increase risk of urinary stone and CKD; ORs and 95 % CIs were 2.73 (1.16, 6.42) and 3.73 (2.50, 5.57) after adjusting for other co-variables. This study revealed that elevated urinary stone and CKD induced by cadmium might increase the risk of urinary stone and CKD.

Keywords Urinary cadmium · Urinary stone · Calciuria and chronic kidney disease

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Cadmium (Cd) is an important toxic metal associated with environmental and industrial pollutant of public health concern due to its wide range of organ toxicity (IPCS 1992; Bernard 2008; Satarug et al. 2010). Long-term exposure to low-dose cadmium has been linked to tubular impairment with a loss of reabsorptive capacity for nutrients, vitamins, and minerals, these included zinc and copper bound to metallothionein (MT), glucose, amino acids, phosphate, calcium, β2-microglobulin (β2-MG), and retinol-binding protein (IPCS 1992). The abnormal urinary excretion of low-molecular-weight proteins, calcium, amino acid, phosphate, glucose and tubular necrosis were observed in cadmium-exposed individuals. In general, the urinary Cd level reflects as a good indicator of excessive Cd exposure and the body burden over long-term exposure before the development of kidney damage (IPCS 1992; Bernard 2008; Satarug et al. 2010). Renal tubular impairment, in addition with osteomalacia and osteoporosis are the clinical signs of the Itai-itai disease in Cd-contaminated populations (Ogawa et al. 2004; Inaba et al. 2005). Kidney and bone damages are the well-known toxic effects of chronic exposure to Cd.

Cd metal is a common by-product during the processing of zinc-bearing ores. In Mae Sot district, Tak province, northwestern Thailand, the cadmium-contaminated areas were caused from the two creeks running through a zinc mine which affected to 13 rural villages of the district. Crops, including rice and vegetable, grown in these areas were found elevated cadmium levels during the surveys in 2001–2004 (National Research for Environmental and Hazardous Waste Management 2005; Pollution Control Department 2004; Simmons et al. 2005). The residents in these villages were agriculturist. Since people consumed rice and other crops grown in those areas, may be at high risk of the cadmium toxicity. In 2004, a population screening survey in those areas found that 554 (7.2 %) had

urinary cadmium levels ≥5 mg/g creatinine. Positive correlations of urinary cadmium levels with renal dysfunction and/or bone toxic effects were found among persons with high cadmium exposure (Honda et al. 2010; Limpatanachote et al. 2009; Nambunmee et al. 2010; Swaddiwudhipong et al. 2010) and no significant correlation between urinary cadmium and urinary stones (Limpatanachote et al. 2009). However, many studies have shown an increased prevalence of urinary stone among workers occupationally exposed to Cd (Jarup and Elinder 1993; Thun et al.1989; Trevisan and Gardin 2005; Nambunmee et al. 2010). In our present study, we determined the association of cadmium exposure with urinary stones formation, hypercalciuria, proteinuria and chronic kidney disease (CKD) in these populations environmentally exposed to cadmium.

Materials and Methods

This cross-sectional study was based on health evaluation. A total 1,085 subjects who were 30 years or older participated in the present study. Five hundred sixty three subjects were randomly selected from 13 cadmium-contaminated villages (during January 2009–January 2010) and 522 subjects of non-cadmium-polluted village located in the same province were selected as the control area. A questionnaire survey was conducted about demographic characteristics, occupational history, residency time, medical history of diabetes, hypertension, renal diseases (including urinary stones and hematuria), cancer and alcohol consumption by trained health workers. We excluded the 82 subjects with known-diabetes, end stage renal failure, cancer, infection and any life threatening diseases from the study. The study protocol was approved by the Ethic committees of Naresuan University (51 02 04 0041). All subjects provided written informed consent and they all agreed to participate and to provide blood and urine sample for follow-up their health check.

Fasting venous blood was collected from all participants. Plasma glucose (Glu), blood urea nitrogen (BUN), electrolyte, serum total calcium (TCal) and urine calcium were measured by using enzymatic colorimetric method, serum and urine creatinine concentration was estimated based on the Jaffe reaction procedures with an auto-analyzer (Konelab 30, Thermo Electron Corporation, Vantaa, Finland) at laboratory of the Mae Sot General Hospital. Urine samples were collected in polyethylene bottles after underwent physical examination, anthropometric measurements and blood taken. A urine sample from each subject was divided into three aliquots (3–5 mL each) one for microscopic analysis and other aliquots were frozen and stored at −20°C for later analysis of cadmium, protein, creatinine and calcium. In which urine for β2-MG determination, prior to the storage, one drop of 0.5 N sodium hydroxide was added to keep the pH to 6–8 for prevented the degradation of β2-MG during storage time. Qualitative tests for pH, protein, glucose, and occult blood were conducted on urine samples at the sampling site using paper strips (Ames test, Bayer, Germany).

Urinary cadmium concentration was determined by a graphite tube atomic-absorption spectrometer (Varian Model AA280Z, USA) at laboratory of the Mae Sot General Hospital. Our laboratory has been certified for toxicological analyses in biological materials by the German External Quality Assessment Scheme.

All participants had clinically normal renal function, defined as a serum creatinine concentration below 159.12 μmol/L (1.8 mg/dL) and serum BUN concentration below 7.14 mmol/L (20 mg/dL). We used the Cockroft-Gault formula to calculate the estimated glomerular filtration rate (eGFR) which incorporates age, body weight and sex (Cockcroft and Gault 1976). The formula is as follows:

$$\text{eGFR} = [(140 - \text{age}) * \text{weight(kg)} * \text{constant}] / \text{serum creatinine } (\mu\text{mol/L})$$

where constant is 1.23 for men and 1.04 for women; serum creatinine in μmol/L.

The classification of eGFR by stages was done according to the Kidney Disease Outcome Quality Initiative (KDOQI) (National Kidney Foundation Kidney Disease Outcome Quality Initiative 2002) criteria as follow: Stage I: normal eGFR (≥90 mL/min/1.73 m^2); Stage II: mildly eGFR (60–89 mL/min/1.73 m^2); Stage III: moderately eGFR (30–59 mL/min/1.73 m^2); Stage IV: severely eGFR (<30 mL/min/1.73 m^2), and Stage V: end-stage renal disease: eGFR (<15 mL/min/1.73 m^2). eGFR lower than 60 mL/min/1.73 m^2 (moderately eGFR) was defined as CKD. The urinary concentration of β2-MG was measured by enzyme immunoassay using GLAZYME β2-microglobulin-EIA test kit (Sanyo Chemical Industries, Ltd., Japan). Urinary protein concentration was measured with the Kingsbury–Clark method. Urinary creatinine concentration was based on the Jaffe reaction. Urinary-calcium (U-Cal) concentration was determined based on the Infinity™ Calcium Arsenazo Liquid Stable Reagent (Thermo Electron, USA).

All participants had a history of urinary stone and/or hematuria or who had hematuria on the urinary microscopic analysis during the survey. The participants underwent X-ray and ultrasonography or an intravenous pyelogram to confirm for urinary stone.

The distributions of variables were expressed in arithmetic mean and standard deviation. Comparisons between groups were performed using the student's t test. Correlation between cadmium exposure index with renal toxicity (urinary levels of protein markers), urinary stone and

urinary calcium were analyzed with Pearson correlation test. Odds ratios (OR) from logistic regression analyses were used to estimate the risk of urinary stone, hypercalciuria, proteinuria, and CKD that was associated with elevated urinary cadmium excretion. The results of all analyses were evaluated for statistical significance using p value <0.05 and the 95 % confidence intervals (CI). All analysis was performed using the SPSS computer program version 13.0 (SPSS, Chicago, IL).

Results and Discussion

A total of 563 residents (aged 55.90 ± 12.02 years) who lived in the cadmium-contaminated villages and 522 residents (aged 54.76 ± 9.85 years) in the non-cadmium contaminated villages participated as control in this study. Of the participants, 369 (34.1 %) were male [161 (43.6 %) were exposed] and 716 (65.9 %) were female [402 (56.1 %) were exposed]. The characteristics of the study population are shown in Table 1. Residents of Cd-exposed were significantly higher in BP, urinary cadmium, β2-MG, urine protein, urine calcium, BUN, urinary stones, smoking and alcohol consumption and lower in BMI, eGFR and HCO^-_3 than residents of non Cd-exposed area ($p < 0.05$).

Urinary cadmium levels showed the positive correlation with β2-MG/g CT ($r = 0.182$, $p < 0.001$), U-Protein/g CT ($r = 0.152$, $p < 0.001$), U-Cal/g CT ($r = 0.299$, $p < 0.001$) and negative correlation with eGFR ($r = -0.124$, $p = 0.003$). While β2-MG/g CT showed the positive correlation with Age ($r = 0.291$, $p < 0.001$), U-Protein/g CT ($r = 0.304$, $p < 0.001$), U-Cal/g CT ($r = 0.517$, $p < 0.001$) and negative correlation with eGFR ($r = -0.538$, $p < 0.001$). U-Protein/g CT showed the positive correlation with Age ($r = 0.161$, $p < 0.001$), U-Cal/g CT ($r = 0.248$, $p < 0.001$) and negative correlation with eGFR ($r = -0.278$, $p < 0.001$). U-Cal/g CT showed the positive correlation with Age ($r = 0.115$, $p = 0.006$), TCal ($r = 0.088$, $p = 0.036$) and negative correlation with eGFR ($r = -0.299$, $p < 0.001$). TCal showed the positive correlation with Age ($r = 0.102$, $p = 0.015$). Glucose showed the positive correlation with Age ($r = 0.119$, $p = 0.005$), β2-MG/g CT ($r = 0.154$, $p < 0.001$) and negative correlation with eGFR ($r = -0.124$, $p = 0.003$). BUN showed the positive correlation with Age ($r = 0.251$, $p < 0.001$), β2-MG/g CT ($r = 0.19$, $p < 0.001$), TCal ($r = 0.094$, $p = 0.026$) and negative correlation with eGFR ($r = -0.279$, $p < 0.001$). CT showed the positive correlation with Age ($r = 0.084$, $p = 0.046$) and negative correlation with TCal ($r = -0.126$, $p = 0.003$) as demonstrated in Table 2. In addition, with Table 3 Multiple logistic regression analyses were used to test an association between urinary cadmium and urinary stones, elevated urine calcium excretion, elevated urine protein excretion and CKD after adjustment with gender, age, smoking and alcohol drinking. As shown in Table 3, the risk of urinary stone OR = 2.73 (95 % CI: 1.16–6.42), elevated urine calcium excretion OR = 1.01 (95 % CI: 1.01–1.02), elevated urine protein excretion OR = 2.05 (95 % CI: 1.24–3.39) and chronic kidney disease OR = 3.73 (95 % CI: 2.50–5.57) by elevated urinary cadmium after adjusted with gender, age, smoking and alcohol drinking.

Table 1 Comparison of general characteristics of the cadmium-exposed with non-exposed population in Mae-Sot district, Tak province

Parameter	Cd-exposed (n = 563) Mean ± SD	Non-exposed (n = 522) Mean ± SD	p value
Age (year)	55.90 ± 12.02	54.76 ± 9.85	0.090
Cd (μg/g CT)	9.75 ± 4.99	1.34 ± 1.42	<0.001
β_2MG (μg/g CT)	422.62 ± 495.78	203.89 ± 249.02	<0.001
U-Protein (mg/g CT)	192.77 ± 240.35	114.74 ± 101.64	<0.001
U-Cal (mg/g CT)	140.83 ± 76.08	85.14 ± 43.36	<0.001
eGFR (mL/min/ 1.73 m^2)	56.38 ± 16.30	71.61 ± 21.12	<0.001
Glucose (mg/dL)	88.59 ± 19.55	88.09 ± 12.36	0.613
BUN (mg/dL)	14.40 ± 5.94	12.02 ± 2.74	<0.001
CT (mg/dL)	1.19 ± 5.25	0.93 ± 0.19	0.237
TCal (mg/dL)	9.99 ± 0.60	10.02 ± 0.43	0.398
Na (mmol/L)	142.01 ± 6.99	142.57 ± 3.12	0.093
K (mmol/L)	4.00 ± 0.59	4.07 ± 0.49	0.055
Cl (mmol/L)	102.15 ± 4.87	102.18 ± 3.06	0.907
HCO^-_3 (mmol/L)	22.75 ± 2.24	24.16 ± 1.75	<0.001
Urinary stone	45 (8.0 %)	11 (2.1 %)	<0.001
Smoking	303 (53.8 %)	111 (21.3 %)	<0.001
Alcohol drinking	261 (46.4 %)	108 (20.7 %)	<0.001

BP blood pressure, *BMI* body mass index, *Cd* cadmium, */g CT* per gram creatinine, *β_2MG* beta 2 microglobulin, *eGFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen, *CT* creatinine, *Na* sodium, *K* potassium, *Cl* chloride, *HCO_3* bicarbonate, *U-protein* urine protein, *U-Cal* urine calcium, *TCal* serum total calcium

In the present study, urinary cadmium concentration was significantly higher in the population of the polluted area than from the control area, which can serve as an indicator of cadmium exposure and body burden. It is well know that both occupational and non-occupational chronic cadmium exposure to Cd can cause kidney damage (IPCS 1992; Bernard 2008; Satarug et al. 2010). An early sign of cadmium-induced nephrotoxicity is the tubular dysfunction, demonstrated by an increased urinary excretion of β2-MG, calciuria, urinary protein, and reduced GFR. The present study revealed a similar correlation between urinary excretion of cadmium and calcium in accordance with other (Staessen et al. 1991; Wu et al. 2001; Hayashi et al. 2003; Schutte et al. 2008). Hypercalciuria is the major risk of stone formation

Table 2 Correlation of all variables among high urine cadmium levels

Correlation between parameters		Correlation coefficient	
		r	*p* value
Cd/g CT	β_2MG/g CT	0.182	<0.001
	U-Protein/g CT	0.152	<0.001
	Cal/g CT	0.299	<0.001
	eGFR	−0.124	0.003
β_2MG/g CT	Age	0.291	<0.001
	U-Protein/g CT	0.304	<0.001
	Cal/g CT	0.517	<0.001
	eGFR	−0.538	<0.001
U-Protein/g CT	Age	0.161	<0.001
	Cal/g CT	0.248	<0.001
	eGFR	−0.278	<0.001
U-Cal/g CT	Age	0.115	0.006
	eGFR	−0.299	<0.001
	TCal	0.088	0.036
TCal	Age	0.102	0.015
Glucose	Age	0.119	0.005
	β_2MG/g CT	0.154	<0.001
	eGFR	−0.124	0.003
BUN	Age	0.251	<0.001
	β_2MG/g CT	0.190	<0.001
	eGFR	−0.279	<0.001
	TCal	0.094	0.026
CT	Age	0.084	0.046
	TCal	−0.126	0.003

Table 3 Impact of the association of elevated urine cadmium excretion with stone, elevated urine calcium excretion urine protein excretion and CKD after adjusted with sex, age, smoke, alcohol drinking

Variables	Elevated urine cadmium excretion		
	OR	95 % CI	*p* value
Urinary stone	2.73	1.16–6.42	0.022
Elevated urine calcium excretion	1.01	1.01–1.02	<0.001
Elevated urine protein excretion	2.05	1.24–3.39	0.005
Chronic kidney disease (CKD)	3.73	2.50–5.57	<0.001
Gender	5.69	3.68–8.81	<0.001
Age	0.95	0.93–0.97	<0.001
Smoking	3.80	2.56–5.64	<0.001
Alcohol drinking	4.68	3.14–6.99	<0.001

(Scheinman 1999; Curhan 2007; Worcester and Coe 2008). In these cadmium-contaminated areas, calcium stones were also observed in 80.0 % of urinary stones analyzed recently (Tosukhowong et al. 2008). Our study revealed a positive association between urinary cadmium and prevalence of urinary stones, after adjusting for other co-variables. Hypercalciuria induced by cadmium might increase the risk of urinary stone formation in this population.

Our study confirmed that both urinary β2-MG and eGFR could be used as sensitive biomarkers of renal tubular dysfunction induced by cadmium. As shown in Table 1, increased excretion of β2-MG in urine or lower eGFR could be observed in individual with elevated urinary cadmium. Our study showed that urinary calcium increased in proportion to these two indicators of renal dysfunction and can reflect early renal dysfunction caused by cadmium. Elevated calcium excretion is reflected both as an early indicator of tubular dysfunction and in relation to the loss of bone minerals. In humans, calcium is mainly excreted by the kidney. It is important for maintaining the normal biological function of cells and is a major component of bone. Many studies have observed hypercalciuria in cadmium-exposed workers and found that calciuria appeared before proteinuria when Wistar rats were injected with cadmium-metallothionein (Friberg 1984; Scott et al. 1978; Jin et al. 1999). Cd-induced hypercalciuria can contribute to not only urinary stone formation, but also bone mineral loss (IPCS 1992; Bernard 2008; Satarug et al. 2010), as seen in Itai-Itai disease (Nogawa and Kido 1993). It can be detected in the early stages of chronic cadmium intoxication. The mechanism underlying the calciuria and the other disorders induced by cadmium is not well understood, but it may be related to changes in renal tubular calcium reabsorption. Both disorders are substantial health problems associated with morbidity and economic costs. Reduced bone mineral density can result in osteomalacia, osteoporosis and an increased risk of bone fractures in the future. Our limitations were not to examine dietary factors as possible risk factors for the urinary stone formation in the present study. In conclusion, cadmium-induced hypercalciuria can contribute to urinary stone formation. Hypercalciuria, proteinuria, elevated β2-MG and reduced eGFR may be related to both renal tubular dysfunction and bone damage caused by cadmium. Then, screening for urinary stones and appropriate treatment should be included in the management program for the reduction of renal damage in this cadmium-exposed population.

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Conflict of interest None.

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