HUMAN HEALTH EFFECTS FROM CADMIUM EXPOSURE: COMPARISON BETWEEN PERSONS LIVING IN CADMIUM-CONTAMINATED AND NON-CONTAMINATED AREAS IN NORTHWESTERN THAILAND

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Abstract. Environmental cadmium contamination is present in some rural villages of Mae Sot District, Tak Province, northwestern Thailand. We compared the health of 751 persons aged ≥ 35 years living in 3 contaminated villages with 682 people from 3 non-contaminated villages with similar socio-demographic and lifestyle characteristics in the same district. All the subjects were screened for urinary cadmium (a biomarker for long-term cadmium exposure), renal function, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, urinary tract stone disease and bone mineral density in 2012. The study renal functions included urinary excretion of β_2-microglobulin (early tubular effect), total urine protein and glomerular filtration rate (glomerular effects). The geometric mean of urinary cadmium level was significantly higher among persons living in the contaminated areas (2.96 μg/g creatinine) than those in the non-contaminated areas (0.60 μg/g creatinine). Persons living in contaminated areas had a significantly higher prevalence of renal dysfunction, bone mineral loss, hypertension and urinary stones than those living in non-contaminated areas. There were no significant differences between the 2 groups in the prevalence of diabetes, hypercholesterolemia and hypertriglyceridemia. This study shows health effects due to environmental cadmium exposure. The prevalences of diabetes, hypercholesterolemia, and hypertriglyceridemia were not associated with cadmium exposure.

Keywords: cadmium, environmental exposure, health effect, Thailand

INTRODUCTION

Cadmium is a widely but sparsely distributed element found in the earth's crust and is primarily association with zinc ore. Cadmium is a common by-product of processing zinc-bearing ore. It is an environmental pollutant of public health concern due to its toxic effects on many organs (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). Dietary cadmium is the major source of exposure for the general non-smoking population. Crops grown in cadmium-contaminated soil can contain elevated cadmium levels (IPCS,

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1992; ATSDR, 2012). Prolonged excessive oral exposure can cause chronic cadmium poisoning. Urinary cadmium excretion is a good measure of long-term cadmium exposure and body burden (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012).

The kidney is a target organ with chronic cadmium exposure (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). An early sign of cadmium-induced nephropathy is tubular proteinuria, usually demonstrated by increased urinary excretion of low molecular weight proteins such as β_2-microglobulin (β_2-MG) and enzymes such as N-acetyl-β-D-glucosaminidase (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). In persons with prolonged exposure to cadmium, tubular dysfunction may progress to glomerular impairment with increased urinary excretion of high molecular weight proteins and a decreased glomerular filtration rate (GFR) (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). Disturbances in calcium and vitamin D metabolism may lead to bone mineral loss (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). Classic cadmium-induced toxicity, known as itai-itai disease in Japan, has been characterized by bone damage accompanied by renal dysfunction (Hagino and Yoshioka, 1961; Inaba *et al*, 2005).

In Mae Sot District, Tak Province, northwestern Thailand, paddy fields are irrigated with the water from two creeks passing through an area where there is a zinc mine that has been actively operating for more than 30 years. Samples of sediment, paddy soil and rice grown in these fields contained markedly elevated cadmium levels during surveys in 2001-2004 (Pollution Control Department, 2004; National Research for Environmental and Hazardous Waste Management, 2005). Concentrations of other toxic substances, such as inorganic arsenic, mercury, and lead in drinking and non-drinking water in those areas were lower than WHO guideline values (Department of Environmental Health, 2013). Cadmium-contamination has been discovered in 12 rural villages in that district (Swaddiwudhipong *et al*, 2007). The majority of residents are farmers and most of them consume rice and other crops grown locally. Food-borne cadmium and tobacco smoking are two main routes of excessive cadmium exposure in this population (Swaddiwudhipong *et al*, 2007, 2010a). Our previous studies among these residents with environmental cadmium exposure revealed a high prevalence of renal dysfunction and some metabolic disorders (Limpatanachote *et al*, 2009; Swaddiwudhipong *et al*, 2010b, 2011, 2012, 2015). However, these health effects are not specific for cadmium toxicity and can be affected by other factors, including socio-demographic characteristics and lifestyle behaviors. Comparison of cadmium-related health effects between persons with similar socio-demographic and lifestyle characteristics who live in contaminated and non-contaminated areas can clarify the cadmium toxic effects in humans. This study compares the health effects of cadmium on persons living in cadmium-contaminated and non-contaminated areas in the same district.

MATERIALS AND METHODS

Study subjects

According to the Thai Primary Health Care Program, persons aged 35 years and older should be screened for some chronic medical disorders including hypertension, diabetes and hypercholesterolemia. Those

aged 50 years and older should also be screened for osteopenia/osteoporosis. The study areas included 3 villages randomly selected from the 12 cadmium-contaminated villages. All persons aged 35 years and older who lived in these 3 contaminated villages were subjects of the study. They were screened for urinary cadmium, renal function, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, urinary stone disease, and bone mineral density (aged ≥ 50 years) in 2012. Renal function testing was comprised of determining urinary excretion of β_2-MG (early tubular effect), urinary total protein, and GFR (glomerular effects). Three villages with similar socio-demographic characteristics were randomly selected from the non-contaminated areas (about 28-40 kilometers from the contaminated villages) in the same district as controls. Rice and drinking and non-drinking water from these non-contaminated areas were checked for cadmium levels and the results were within normal limits.

For participant information was obtained about demographic characteristics, alcohol consumption, tobacco smoking, rice consumption, and history of hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia and renal disease (including urinary stones and hematuria) by trained health workers. Heights and weights were measured to obtain body mass index (kg/m^2). Blood pressures were measured twice in the right arm in a sitting position and the average was recorded. Hypertension was defined as diastolic pressure ≥ 90 mmHg and/or systolic pressure ≥ 140 mmHg or current use of antihypertensive medication (Thai Hypertension Society, 2012).

Ethical considerations

The Tak Provincial Health Office Ethics Committee approved this study protocol (Tak 2/2555, 16 March 2012) and oral informed consent was obtained from the villagers before they participated in the survey.

Laboratory analysis

Fasting venous blood was collected from each participant and forwarded to the laboratory of Mae Sot General Hospital within 2 hours of collection for analysis of plasma glucose by the enzymatic colorimetric method, serum creatinine by the Jaffe reaction method and serum total cholesterol and triglycerides by the enzymatic colorimetric method. The samples were examined using an auto-analyzer (Konelab 30, Thermo Electron Corporation, Vantaa, Finland). Quality assurance was confirmed via simultaneous analysis of reference serum Nortrol® and Abtrol® (Thermo Fisher Scientific Oy, Vantaa, Finland). Persons who had fasting plasma glucose ≥ 126 mg/dl received repeat testing 2-4 weeks after the first measurement. Diabetes was defined as a fasting plasma glucose ≥ 126 mg/dl on 2 occasions or currently receiving diabetic medication (Diabetes Association of Thailand, 2011). The GFR was estimated from the serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation (National Kidney Foundation, 2002). Hypercholesterolemia was defined as total serum cholesterol level ≥ 200 mg/dl or currently taking cholesterol-lowering medication and hypertriglyceridemia was defined as a serum triglyceride level ≥ 200 mg/dl or currently taking triglyceride-lowering medication (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002).

A 30-ml sample of a second morning urine was obtained from each participant. Two 3-ml aliquots from each urine sample were frozen (-20°C) until analysis for

cadmium and β_2-MG within 2 weeks of collection. Prior to storage, one drop of 0.5N sodium hydroxide was added to one of the two aliquots to adjust the urine pH to 6-8 to prevent degradation of the β_2-MG in an acid condition. The rest of the urine sample was used for microscopic analysis and biochemistry measurements.

The urinary cadmium content was determined using a graphite tube atomic-absorption spectrometer (Varian Model AA280Z, Palo Alto, CA). Quality assurance was confirmed by simultaneous analysis of reference urine Lyphocheck® (Bio-Rad, Gladesville, New South Wales, Australia). The urinary β_2-MG concentration was determined using an enzyme-linked fluorescent assay (BioMerieux, Marcy l'Etoile, France). The total urine protein content was measured using a colorimetric method. The urine creatinine level was determined using the Jaffe reaction method to adjust for urinary excretion of cadmium and study markers. Quality assurance was confirmed by simultaneous analysis of reference urine uTrol® and uTrol High® (Thermo Fisher Scientific Oy, Vantaa, Finland).

Bone mineral density was measured using a dual-energy x-ray absorptiometry bone scanner (Lunar PIXI, Madison, WI) at the distal non-dominant forearm of each participant aged 50 years or older. Osteoporosis was defined as bone mineral density of ≥2.5 standard deviations below the mean for women aged 20-29 years and osteopenia was defined as bone density between 1 and 2.5 standard deviations below the mean for woman aged 20-29 years (WHO, 2003).

Participants with a history of hematuria, a urinary stone or with hematuria on urine analysis were screened for the presence of a urinary tract stone by plain x-ray and ultrasonography or an intravenous pyelogram. The prevalence of urinary tract stones was determined by either a history of having been diagnosed with having a urinary tract stone or finding one on examination.

Statistical analysis

The EpiInfo™ version 7 was used to analyze the study data. The variable distributions were expressed in percentages. The arithmetic mean and standard deviation were used for the quantitative variables. The geometric mean was used when the logarithms of the observations were more likely to distribute normally than the observations themselves. The chi-square test was used for comparing between proportions and analysis of variance and the Mann-Whitney *U* test was used to compare means.

RESULTS

There were 808 persons aged ≥35 years living in the 3 cadmium-contaminated villages and 717 in the 3 non-contaminated villages. A total of 751 persons (92.9%) in the contaminated villages and 682 (95.1%) in the non-contaminated villages participated in the screening program. Three point six percent of those in the contaminated villages and 2.9% of those in the non-contaminated villages refused to be screened and claimed they were healthy. The other non-participants were absent or could not be contacted at the time of the survey.

Table 1 shows the characteristics of the respondents in each sample. The socio-demographic characteristics in the contaminated and non-contaminated villages were similar. There were no significant differences between the 2 groups (contaminated and non-contaminated) by sex, age, education, occupation, al-

Table 1
Characteristics of the study subjects aged ≥ 35 years living in cadmium-contaminated and non-contaminated areas.

Characteristics	Contaminated areas	Non-contaminated areas	*p*-value
Total no. surveyed	751	682	
Sex			
Male (%)	42.3	46.0	0.159
Female (%)	57.7	54.0	
Age (years)			
Mean ± SD[a]	54.8 ± 11.8	55.5 ± 11.5	0.261
Education			
Primary school (%)	78.2	77.0	0.592
Greater than primary school (%)	21.8	23.0	
Occupation			
Agriculture (%)	84.7	87.8	0.085
Other (%)	15.3	12.2	
Alcohol consumption			
Never (%)	41.3	43.4	
Former (%)	23.7	20.1	0.256
Current (%)	35.0	36.5	
Smoking status			
Never (%)	45.5	45.0	
Former (%)	24.5	20.4	0.078
Current (%)	30.0	34.6	
Rice consumption			
Rice grown in contaminated areas (%)	71.2	0.9	< 0.001
Rice grown in (purchased from) other areas (%)	28.8	99.1	
Body mass index (kg/m^2)			
Mean ± SD[a]	22.3 ± 3.8	22.7 ± 3.4	0.067

[a]Arithmetic mean ± standard deviation.

cohol consumption, smoking status and body mass index. Seventy-one point two percent of persons in the contaminated villages reported consuming rice grown locally compared to 0.9% in the non-contaminated villages.

The proportion of persons with a urinary cadmium level ≥ 2 μg/g-creatinine was significantly higher in the contaminated areas (66.7%) than in the non-contaminated areas (5.1%) (Table 2). The geometric mean urinary cadmium level was higher among persons living in the contaminated villages (2.96 μg/g-creatinine) than those in the non-contaminated villages (0.60 μg/g-creatinine). Persons in the contaminated areas had significantly higher prevalence of urinary β_2-MG ≥ 300 μg/g-creatinine (36.1%) than those in the non-contaminated areas (28.3%). The geometric mean level of urinary β_2-MG was higher among persons in contaminated areas than among those in the non-contaminated areas. Significantly higher urinary total protein level and lower GFR were found among persons in contaminated areas than those in non-con-

Table 2
Urinary cadmium level and renal function among persons living in cadmium-contaminated and non-contaminated areas.

Markers	Contaminated areas	Non-contaminated areas	*p*-value
Total no. surveyed	751	682	
Urinary cadmium (μg/g cr)			
≥ 2 (%)	66.7	5.1	< 0.001
Mean ± SD[a]	2.96 ± 2.46	0.60 ± 2.19	< 0.001
Urinary β2-microglobulin (μg/g cr)			
≥ 300 (%)	36.1	28.3	0.002
Mean ± SD[a]	286.0 ± 5.8	194.7 ± 3.9	< 0.001
Urinary total protein (mg/g cr)			
≥ 200 (%)	24.1	17.2	< 0.001
Mean ± SD[a]	130.4 ± 2.2	113.9 ± 2.2	0.001
Glomerular filtration rate (ml/min/1.73 m^2)			
< 60 (%)	16.2	10.1	< 0.001
Mean ± SD[b]	75.7 ± 18.7	78.8 ± 16.5	0.002

[a]Geometric mean ± geometric standard deviation.
[b]Arithmetic mean ± standard deviation.

Table 3
Bone density and prevalence of metabolic diseases in subjects living in cadmium-contaminated and non-contaminated areas.

Markers	Contaminated areas	Non-contaminated areas	*p*-value
Total no. surveyed	751	682	
Forearm bone density (g/cm^2)[a]			
Osteopenia/osteoporosis (%)	54.4	45.3	0.006
Mean ± SD[b]	0.396 ± 0.093	0.411 ± 0.107	0.021
Hypertension (%)	32.5	21.8	< 0.001
Diabetes (%)	5.5	6.5	0.427
Urinary stone (%)	10.4	5.0	< 0.001
Hypercholesterolemia (%)	21.0	24.5	0.120
Hypertriglyceridemia (%)	17.6	18.8	0.559

[a]Among persons aged ≥50 years; [b]Arithmetic mean ± standard deviation.

taminated areas. The prevalence of a GFR <60 ml/min/1.73 m^2 (chronic kidney disease stages 3-5) was significantly greater among persons from contaminated areas (16.2%) than among those from non-contaminated areas (10.1%).

Persons from contaminated areas had significantly greater prevalences of osteopenia/osteoporosis, hypertension and urinary stone disease than those from non-contaminated areas (Table 3). The mean bone mineral density was lower

among persons from contaminated villages than those from non-contaminated villages. There were no significant differences between the 2 samples in the prevalence of diabetes, hypercholesterolemia and hypertriglyceridemia.

DISCUSSION

The kidney can be affected by chronic cadmium exposure. The GFR is a good indicator for the severity of chronic kidney disease (National Kidney Foundation, 2002). The earliest manifestation of cadmium-induced nephropathy is an increase in urinary excretion of low molecular weight proteins due to impaired tubular reabsorption (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). Among these proteins, β_2-MG has been one of the most validated markers for screening of cadmium nephrotoxicity. In persons with prolonged exposure to excessive cadmium levels, tubular impairment may progress to glomerular dysfunction with increased urinary excretion of high molecular weight proteins and decreased GFR (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Satarug *et al*, 2010; ATSDR, 2012). The present study demonstrated that persons living in contaminated areas have a significantly greater urinary excretion of β_2-MG and total protein, and a lower GFR than those in non-contaminated areas. These findings suggest environmental cadmium exposure affects both tubular and glomerular function.

Loss of bone mineral density can lead to osteopenia and osteoporosis, which increase the risk for fracture, giving rise to significant morbidity and some mortality (WHO, 2003). A relationship between prolonged excessive exposure to cadmium and decreased bone mineral density has been shown in environmentally exposed populations, which may be due to disturbance in renal metabolism of vitamin D, increased urinary excretion of calcium and a direct effect on bone resorption (IPCS, 1992; Bernard, 2008; Järup and Akesson, 2009; Limpatanachote *et al*, 2010; Nambunmee *et al*, 2010; Satarug *et al*, 2010 ATSDR, 2012). The present study found persons aged ≥ 50 years living in contaminated areas had significantly lower bone density and had a higher prevalence of osteopenia/osteoporosis than those in non-contaminated areas. This study shows the importance of screening and management of bone mineral loss in persons with prolonged excessive cadmium exposure, particularly in the elderly.

Hypertension has long been recognized as a major risk factor for cardiovascular disease. Some recent epidemiologic studies have found positive associations between body cadmium levels and hypertension (Whittemore *et al*, 1991; Pizent *et al*, 2001; Al-Saleh *et al*, 2006; Satarug *et al*, 2006; Eum *et al*, 2008; Tellez-Plaza *et al*, 2008; Swaddiwudhipong *et al*, 2010b; Lee and Kim, 2012) but some found no association (Staessen *et al*, 1991a, 1993; Kurihara *et al*, 2004; Sirivarasai *et al*, 2004). These inconsistent findings might be due to different study subjects and methodological limitations, such as small sample size, suboptimal subject selection and lack of adjustment for other potential risk factors. However, recent studies using data from the US and Korean National Health and Nutrition Examination Survey (NHANES) found a positive association between elevated blood cadmium and hypertension (Eum *et al*, 2008; Tellez-Plaza *et al*, 2008; Lee and Kim, 2012). Our previous survey of persons living in the cadmium-contaminated villages demonstrated higher cadmium levels in the urine

were associated with a higher prevalence of hypertension after adjusting for other potential confounders (Swaddiwudhipong *et al*, 2010b). The present study found a significantly higher prevalence of hypertension among persons living in contaminated areas than those living in non-contaminated areas. Our study confirms the hypothesis that environmental exposure to cadmium can increase the prevalence of hypertension. Although an elevated cadmium level-elevated blood pressure correlation and possible mechanisms have been found in animal studies (IPCS, 1992; ATSDR, 2012), the mechanism by which cadmium induces hypertension in human remains unclear and requires further study.

Excessive urinary excretion of calcium is a major risk factor for stone formation (Curhan *et al*, 2001; Curhan, 2007; Worcester and Coe, 2008). Many studies of populations with environmental cadmium exposure have found a positive correlation between urinary cadmium and calciuria (Staessen *et al*, 1991b; Wu *et al*, 2001; Hayashi *et al*, 2003; Schutte *et al*, 2008; Swaddiwudhipong *et al*, 2011). In our previous study among persons living in cadmium contaminated areas, urinary cadmium was found to correlate significantly with the prevalence of urinary stones and urinary calcium (Swaddiwudhipong *et al*, 2011). The present study showed that persons living in cadmium contaminated areas were significantly more likely to have urinary stones than those who did not. This study confirms the greater prevalence of urinary stones from environmental cadmium exposure.

Few human studies have shown associations between cadmium exposure and diabetes, hypercholesterolemia, and hypertriglyceridemia. Using data from the 1988-1994 US NHANES, Schwartz *et al* (2003) found a positive relationship between urinary cadmium and the prevalence of impaired fasting glucose and diabetes. A study using data from the 2005-2010 Korean NHANES found an association between blood cadmium and metabolic syndrome in men but not in women (Lee and Kim, 2012). No other studies demonstrated these effects in humans exposed to cadmium. In the present study, the prevalence rates of diabetes, hypercholesterolemia and hypertriglyceridemia were not different between persons living in cadmium contaminated and non-contaminated areas. We conclude that the risk for these metabolic disorders in relation to cadmium exposure remains uncertain in our study areas.

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