Cadmium-Exposed Population in Mae Sot District, Tak Province: 4 Bone Mineral Density in Persons with High Cadmium Exposure

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Objective: *To measure bone mineral density in cadmium-exposed persons aged 40 years and older that lived in the 12 contaminated villages in northwestern Thailand.*

Material and Method: *Five hundred seventy three persons with urinary cadmium levels $\geq$ 5 μg/g creatinine during the 2004-2006 surveys were screened in 2007 for urinary excretion of cadmium, bone formation and resorption markers, and renal function markers. Calcaneus bone density was measured in each person by a dual-energy X-ray absorptiometry bone scanner.*

Results: *The mean age of the study persons was 57 years old. The geometric mean level of urinary cadmium for women was significantly higher than that for men. Women had a lower mean of calcaneus bone density than men. The rate of osteoporosis in women (21.5%) was significantly higher than that for men (14.7%). Calcaneus bone density was negatively correlated with urinary excretion of calcium (in both genders) and crosslinked N-telopeptide of type I collagen (in women), after adjusting for other co-variables. Increasing urinary cadmium levels appeared to correlate with reduced bone density in women, but not in men. In both genders, urinary excretion of β_2-microglobulin and N-acetyl-β-D-glucosaminidase was higher in persons with osteoporosis than those without.*

Conclusion: *Bone mineral loss is correlated with urinary cadmium levels and renal dysfunction in this female population.*

Keywords: *Cadmium, Urinary cadmium, Bone mineral density, Osteoporosis, Renal dysfunction*

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Cadmium is a widely but sparsely distributed element found in the earth's crust, primarily in association with zinc ores. Cadmium is a common by-product during the processing of zinc-bearing ores. Cadmium is an important public health concern due to its toxic effects to many organs[1-6]. The major 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[1,4]. Prolonged excessive oral exposure can cause chronic cadmium poisoning. High cadmium content is also presented in tobacco leaves, contributing further cadmium exposure for smokers. Urinary cadmium excretion is a good measure for prolonged cadmium exposure and body burden[1-6].

The kidney is considered the critical target organ for chronic exposure to cadmium. 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), retinol binding protein, α_1-microglobulin, enzymes such as N-acetyl-β-D-glucosaminidase (NAG), and calcium. Long-term

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exposure to cadmium, tubular dysfunction may progress to glomerular damage with increased blood creatinine and decreased glomerular filtration rate[1-6]. The disturbances of calcium and vitamin D metabolism may lead to bone mineral loss[1-6]. Classic cadmium-related bone toxicity, which is known as itai-itai disease in Japan, has been characterized by bone pain, severe osteomalacia or osteoporosis and multiple bone fractures, accompanied with renal dysfunction[7,8].

In Mae Sot District, Tak Province, north-western Thailand, some rice fields were irrigated with water from two creeks running through a zinc mine that was operated for more than 20 years. Crops, including rice, grown in the areas were found to contain markedly elevated cadmium levels during the surveys in 2001-2004[9-11]. The cadmium-contaminated areas were discovered in the 12 villages of the district. Since the majority of inhabitants consumed locally grown rice and other crops, they were at risk of cadmium-induced toxicity. A population screening survey for cadmium exposure using urinary cadmium measurement was conducted in 2004 among inhabitants aged 15 years and older living in these cadmium-contaminated villages. Of the 7,697 adults examined, 7.2% had urinary cadmium levels $\geq$ 5 µg/g creatinine[12]. A significant proportion of those with high cadmium exposure had renal dysfunction[13-15]. Increased urinary excretion of bone resorption markers was also found in elderly persons with high exposure to cadmium[16]. This report presents bone mineral density in highly exposed persons aged 40 years and older that lived in these contaminated areas.

Material and Method

Study population

The present study included 573 persons aged 40 years and older that lived in the 12 cadmium-contaminated villages and had urinary cadmium levels $\geq$ 5 µg/g creatinine during the screening surveys in 2004-2006. The participants were screened for urinary cadmium, bone formation and resorption markers, renal function markers, and bone mineral density in 2007. Selected renal function markers were urinary excretion of β_2-MG, NAG and calcium, serum creatinine and calcium. Bone markers included serum osteocalcin (bone formation marker) and urinary excretion of crosslinked N-telopeptide of type I collagen (NTx) (bone resorption marker). The present study protocol was approved by the Mae Sot Hospital Ethical Committee and oral informed consent was obtained from the study persons before they participated in the survey.

Survey

Each participant was interviewed about demographic characteristics, smoking status, alcohol consumption, and medical history of chronic diseases by trained health workers. Fasting venous blood was collected from each participant and forwarded to the laboratory of Mae Sot General Hospital within two hours of collection. Plasma glucose and serum calcium were measured by the enzymatic colorimetric method. Serum creatinine was determined by the Jaffe reaction method. The samples were measured by using an automated analyzer (Konelab 30, Thermo Electron Corporation, Finland). The laboratory of the hospital was certified for clinical chemistry analysis by the National External Quality Assessment Scheme in Clinical Chemistry, Thailand Ministry of Public Health, and by the External Quality Assessment in Clinical Chemistry, Faculty of Medical Technology, Mahidol University. Diabetes was defined as fasting plasma glucose $\geq$ 126 mg/dl on two occasions or currently receiving antidiabetic treatment. Serum osteocalcin was measured by the immunoradiometric assay.

A 30-ml sample of second morning urine was obtained from each participant. Two 3 ml aliquots from each urine sample were kept frozen (-20°C) for analysis of cadmium, β_2-MG, NAG, and NTx by the Department of Social and Environmental Health, Kanazawa Medical University, Japan. Prior to the storage, one drop of 0.5N 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 forwarded to the laboratory of Mae Sot General Hospital for measurement of calcium and creatinine.

The urinary cadmium content was determined by a flameless atomic-absorption spectrometer (Shimadzu Model AA-6300, Japan). Urinary β_2-MG concentration was determined by the latex agglutination immunoassay (Eiken Chemical, Japan) and NAG content was determined by the colorimetric assay (Shionogi Pharmaceuticals, Japan). Urinary calcium concentration was measured by the colorimetric method and NTx was measured by the competitive enzymatic immunoassay. Urinary creatinine concentration by the Jaffe reaction method was used to adjust for urinary excretion of cadmium and the study markers.

Body weight (kg) and bone mineral density (g/cm^2) were measured in each participant. Calcaneus bone density was determined by a dual-energy X-ray absorptiometry bone scanner (Lunar PIXI, USA).

Osteoporosis was defined as bone mineral density of 2.5 standard deviations or more below the young adult mean (T-score $\leq$ -2.5). The measurement used adults aged 20-50 years old as the reference population.

Statistical analysis

The distributions of variables were expressed in percentages of the study persons. The arithmetic mean and standard deviation were used to summarize 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 comparison between proportions. The analysis of variance or the Mann-Whitney U test was used for comparison between means. Multiple linear regression analysis was used to identify the determinants of bone mineral density in the study persons.

Results

The characteristics of the 573 study persons are shown in Table 1. The mean age of them was 57 years old. The male to female ratio was 1:1.7. There were significant differences between men and women in tobacco smoking, alcohol consumption, and body weight. The geometric mean level of urinary cadmium for women was significantly higher than that for men. Women had a lower mean of calcaneus bone density than men. The prevalence rate of osteoporosis in these persons was 19.0%. The rate of osteoporosis in women (21.5%) was significantly higher than that for men (14.7%).

Table 2 presents characteristics and markers of renal and bone effects in persons with osteoporosis, compared to those without osteoporosis. In men, those with osteoporosis had significantly higher means of age, serum creatinine and osteocalcin, urinary excretion of β_2-MG, NAG and NTx than those without osteoporosis. In women, those with osteoporosis had significantly higher means of age, serum calcium and osteocalcin, urinary excretion of β_2-MG, NAG and NTx than those without osteoporosis. In both genders, the mean weight level was significantly lower in persons with osteoporosis than those without osteoporosis. The mean urinary cadmium level in women with osteoporosis was higher than those without osteoporosis.

Table 3 presents the correlations of calcaneus bone density with study variables including age,

Table 1. Characteristics of the study persons, by gender

Characteristics	Total	Male	Female	p-value*
Total No. surveyed	573	211	362	
Age (years)				
Mean $\pm$ SD**	57.3 $\pm$ 11.3	58.7 $\pm$ 12.4	56.6 $\pm$ 10.6	0.07
Smoking status				
Never (%)	28.3	5.7	41.4	<0.01
Former (%)	32.8	35.1	31.5	
Current (%)	38.9	59.2	27.1	
Alcohol consumption				
Never (%)	37.5	3.3	57.5	<0.01
Former (%)	26.9	42.7	17.7	
Current (%)	35.6	54.0	24.9	
Body weight (kg)				
Mean $\pm$ SD**	51.9 $\pm$ 10.2	54.1 $\pm$ 9.5	50.6 $\pm$ 10.4	<0.01
Urinary cadmium (μg/g creatinine)				
Mean $\pm$ SD***	7.9 $\pm$ 1.5	7.5 $\pm$ 1.5	8.2 $\pm$ 1.6	0.03
Calcaneus bone density (g/cm^2)				
Mean $\pm$ SD**	0.41 $\pm$ 0.11	0.46 $\pm$ 0.10	0.38 $\pm$ 0.11	<0.01
Osteoporosis (%)	19.0	14.7	21.5	0.04

* Differences between males and females
** Arithmetic mean $\pm$ standard deviation
*** Geometric mean $\pm$ standard deviation

Table 2. Characteristics of the study persons with and without osteoporosis, by gender

Characteristics	Male			Female		
	No (n = 180)	Osteoporosis (n = 31)	p-value	No (n = 284)	Osteoporosis (n = 78)	p-value
Age (years)						
Mean ± SD*	56.9 ± 11.6	69.3 ± 11.3	<0.01	53.6 ± 9.1	67.2 ± 8.6	<0.01
Body weight (kg)						
Mean ± SD*	55.2 ± 9.5	47.9 ± 6.8	<0.01	53.2 ± 9.4	41.2 ± 8.3	<0.01
Serum creatinine (mg/dl)						
Mean ± SD*	1.17 ± 0.37	1.36 ± 0.50	<0.01	0.93 ± 0.29	1.01 ± 0.36	0.22
Serum calcium (mg/dl)						
Mean ± SD*	9.4 ± 0.5	9.2 ± 0.9	0.15	9.4 ± 0.6	9.6 ± 0.5	<0.01
Serum osteocalcin (ng/ml)						
Mean ± SD*	5.4 ± 2.6	7.0 ± 3.1	<0.01	5.5 ± 3.4	7.7 ± 3.9	<0.01
Urinary cadmium (μg/g creatinine)						
Mean ± SD**	7.8 ± 1.5	7.4 ± 1.3	0.93	8.2 ± 1.6	8.6 ± 1.5	0.08
Urinary calcium (mg/g creatinine)						
Mean ± SD**	67.0 ± 2.4	74.1 ± 3.0	0.58	78.4 ± 2.5	88.9 ± 3.0	0.31
Urinary β_2-MG (μg/g creatinine)						
Mean ± SD**	369.6 ± 9.4	1,419.0 ± 12.3	<0.01	170.0 ± 6.0	396.6 ± 7.4	<0.01
Urinary NAG (unit/g creatinine)						
Mean ± SD**	5.2 ± 1.8	8.2 ± 1.9	<0.01	5.6 ± 1.8	7.2 ± 1.7	<0.01
Urinary NTx (nM BCE/mmol creatinine)						
Mean ± SD**	42.3 ± 1.7	52.4 ± 1.8	0.04	50.4 ± 1.9	75.4 ± 1.7	<0.01
Diabetes (%)	3.3	3.2	0.97	8.8	6.4	0.50

* Arithmetic mean ± standard deviation

** Geometric mean ± standard deviation

β_2-MG = β_2-microglobulin; NAG = N-acetyl-β-D-glucosaminidase; NTx = crosslinked N-telopeptide of type I collagen

alcohol consumption, tobacco smoking, body weight, prevalence of diabetes, urinary cadmium, and bone biomarkers by multiple linear regression analysis. In both genders, calcaneus bone density significantly decreased with age, urinary calcium excretion, and decreasing weight. Increases in urinary NTx and cadmium were correlated with decreased calcaneus bone density in women, but not in men.

Discussion

The maintenance of a normal, mechanically competent skeletal mass depends on keeping the process of bone resorption and formation (bone remodeling) in balance. Failure to match bone formation with bone resorption results in net bone mineral loss. Many studies have found an association between increasing body cadmium levels and bone mineral loss[1-7]. The possible mechanisms for cadmium-related bone loss include hypercalciuria caused by cadmium-induced renal tubular damage, altering vitamin D metabolism, interference with calcium absorption in the gut and deposition in bone, and primary effects on bone[17-20]. The authors' previous study among elderly persons living in these contaminated villages found positive correlations of urinary cadmium with increasing urinary excretion of NTx (a bone resorption marker), calcium, and renal tubular markers (β_2-MG and NAG), suggesting possible links of cadmium exposure with bone toxic effect and renal dysfunction[16]. The present study revealed negative correlations of calcaneus bone density with urinary excretion of calcium (in both genders) and NTx (in women), after adjusting for other co-variables. In the present study, increasing urinary cadmium levels appeared to correlate with reduced bone density in women although the correlation was not statistically significant ($p = 0.08$). Urinary excretion of β_2-MG and NAG was higher in persons with osteoporosis than those without osteoporosis. These findings support the correlations of bone mineral loss with cadmium

Table 3. Multiple linear regression analysis of the determinants of calcaneus bone density, by gender

Independent variables*	Calcaneus bone density (g/cm^2)			
	Male		Female	
	β**	p-value	β**	p-value
Age	-0.002	<0.01	-0.005	<0.01
Alcohol consumption	0.014	0.68	0.007	0.43
Tobacco smoking	-0.032	0.23	-0.006	0.53
Body weight	0.004	<0.01	0.004	<0.01
Diabetes	-0.018	0.59	-0.013	0.35
Serum osteocalcin	-0.000	0.94	-0.000	0.78
Urinary calcium	-0.000	<0.01	-0.000	0.04
Urinary cadmium	-0.000	0.33	-0.001	0.08
Urinary NTx	-0.000	0.404	-0.001	<0.01
R^2	0.33		0.61	

*Age (years), alcohol consumption (never = 0, ever = 1), tobacco smoking (never = 0, ever = 1), body weight (kg), diabetes (no = 0, yes = 1), serum osteocalcin (ng/ml), urinary calcium (mg/g creatinine), urinary cadmium (μg/g creatinine), urinary NTx (nM BCE/mmol creatinine)
** β = Regression coefficient

exposure and renal dysfunction in the exposed female population.

In a nation-wide survey during 2000-2001, the prevalence of osteoporosis in Thai women aged 40-80 years old was 13.6 % for femoral neck and 19.8 % for lumbar spine(21). In a recent survey in one northeastern province, the rate of osteoporosis among rural Thai men aged 40 years and older was 12.4 % for femoral neck, 5.4 % for lumbar spine, and 4.3 % for both sites(22). The prevalence rate of osteoporosis in the study persons was higher than those detected in other areas of the country(21-24). Dissimilar findings might be due to differences in study subjects, measurements, and risk factors such as body weight, dietary calcium intake, and endocrine factors. However, high cadmium exposure might increase risk of bone mineral loss in these study persons.

Advancing age and low body weight are common risk factors for bone mineral loss(25). The present study similarly found negative correlations of bone mineral density with age and low body weight. In the present study, lower bone density was observed in women than men. Women are more likely to have bone mineral loss than men due to endocrine factors, menstruation, and pregnancy. Higher cadmium levels in the study women than men might contribute to further risk of bone mineral loss. Since the morbidity of low bone density is associated with increased risk of fractures and serious functional impairment, the elderly women, particularly those with leanness, in these cadmium-contaminated areas should be the primary target for assessment of cadmium-related bone toxic effects.

The present study had some limitations. The present study examined only those with high urinary cadmium levels and did not include other possible risk factors for lower bone mineral density. Further population studies including possible risk factors for bone loss among those with various urinary cadmium levels may be useful to clarify the strength of cadmium-induced bone toxic effects in this exposed population.

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การได้รับสารแคดเมียมในประชากรอำเภอแม่สอดจังหวัดตาก: 4 ความหนาแน่นของกระดูกในผู้ที่สัมผัสสารแคดเมียมสูง

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***วัตถุประสงค์**: เพื่อศึกษาความหนาแน่นของกระดูกในประชากรอายุ 40 ปี ขึ้นไปซึ่งสัมผัสสารแคดเมียมสูง และอาศัยอยู่ในพื้นที่ปนเปื้อนสารแคดเมียมรวม 12 หมู่บ้าน ในพื้นที่ตะวันตกเฉียงเหนือของประเทศไทย*
***วัสดุและวิธีการ**: กลุ่มประชากรตัวอย่างจำนวน 573 ราย ที่มีระดับแคดเมียมในปัสสาวะ ≥ 5 ไมโครกรัม/กรัมครีเอตินิน จากการสำรวจในช่วงปี พ.ศ. 2547-2549 ได้รับการตรวจในปี พ.ศ. 2550 เพื่อหาระดับแคดเมียมในปัสสาวะ ความผิดปกติของการสร้างกระดูก และการทำงานของไต รวมทั้งได้รับการตรวจความหนาแน่นของกระดูกส้นเท้าด้วยเครื่อง dual-energy x-ray absorptiometry scanner*
***ผลการศึกษา**: ประชากรที่ศึกษามีอายุเฉลี่ยประมาณ 57 ปี เพศหญิงมีค่าเฉลี่ยเรขาคณิต ของระดับแคดเมียมในปัสสาวะสูงกว่าเพศชาย แต่มีค่าเฉลี่ยของความหนาแน่นของกระดูกต่ำกว่าเพศชาย อัตราความชุกของกระดูกพรุนในเพศหญิงเท่ากับร้อยละ 21.5 ซึ่งสูงกว่าร้อยละ 14.7 ในเพศชาย ความหนาแน่นของกระดูกส้นเท้าพบว่าลดลงเมื่อระดับแคลเซียมในปัสสาวะเพิ่มขึ้น (พบทั้งเพศชายและหญิง) และเมื่อระดับ crosslinked N-telopeptide of type I collagen ในปัสสาวะเพิ่มขึ้น (พบเฉพาะเพศหญิง) รวมทั้งพบว่าเมื่อระดับแคดเมียมในปัสสาวะเพิ่มขึ้นความหนาแน่นของกระดูกจะลดลงซึ่งพบเฉพาะเพศหญิง การขับ β_2-microglobulin และ N-acetyl-β-D-glucosaminidase ในปัสสาวะซึ่งเป็นตัวชี้วัดความผิดปกติของไต พบเพิ่มสูงขึ้นในกลุ่มที่มีกระดูกพรุนมากกว่ากลุ่มที่ไม่มีกระดูกพรุน ซึ่งพบทั้งเพศชายและหญิง*
***สรุป**: ความหนาแน่นของกระดูกที่ลดลง มีความสัมพันธ์กับระดับแคดเมียมในปัสสาวะ และความผิดปกติของไตในประชากรเพศหญิงที่สัมผัสสารแคดเมียมนี้*