Cadmium and Lead in Blood in Relation to Low Bone Mineral Density and Tubular Proteinuria

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Long-term exposure to cadmium may cause kidney and bone damage. Urinary cadmium is commonly used as the dose estimate for the body burden of cadmium. However, elevated levels of cadmium in the urine may reflect not only high levels of cadmium dose but also renal dysfunction. In this study we used blood cadmium as the dose estimate. In addition, we analyzed blood lead. We examined 479 men and 542 women, ages 16–81 years, who were environmentally or occupationally exposed to cadmium and lead. We used urinary protein α_1-microglobulin as a marker for tubular proteinuria and measured forearm bone mineral density using dual-energy X-ray absorptiometry. The relationship between blood cadmium and tubular proteinuria was strong, even when we excluded occupationally exposed participants. The subgroup with the highest blood cadmium levels had a 4-fold risk of tubular proteinuria compared to the subgroup with the lowest blood cadmium levels. In the older age group (age > 60), the risk of low bone mineral density (z-score < –1) for the subgroup with the highest blood cadmium levels was almost 3-fold compared to the group with lowest blood cadmium levels. We found no similar associations for lead. The observed effects may be caused by higher cadmium exposure in the past. This study strengthens previous evidence that cadmium exposure may affect both bone mineral density and kidney function. *Key words:* **bone density, cadmium, environmental exposure, heavy metals, lead, occupational exposure, osteoporosis, proteinuria.** *Environ Health Perspect* **110:699–702 (2002). [Online 3 June 2002]**
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Long-term exposure to cadmium may cause kidney and bone damage (*1*); the most well-known example is the itai-itai disease in Japan. In two earlier studies (*2,3*) we showed that cadmium affects kidneys and bone at lower levels than previously anticipated. We also found a relationship between tubular damage and osteoporosis. In these earlier studies urinary cadmium was used as the dose estimate for cadmium. Urinary cadmium is commonly used to assess body burden of cadmium and has been useful in many studies (*4*). However, it has been claimed that elevated levels of cadmium in the urine may reflect not only high levels of cadmium dose but also renal damage (*1,5,6*). Cadmium in blood mainly reflects recent exposure, but it has also been shown to be a good indicator of cadmium body burden (*7,8*).

It is well documented that lead can disturb hemoglobin synthesis and cause behavioral and neurologic disturbances in children (*9*). Some epidemiologic studies have also indicated that lead can impair kidney function (*10,11*). Chronic, low-level exposure to lead has been associated with increased excretion of low-molecular-weight proteins and lysosomal proteins. Lead is actively taken up and incorporated in the bone. More than 90% of the total human body burden of lead is in the bone (*12*), and lead is also suspected to cause bone damage (*13*). Lead in blood is the most frequently used dose estimate for lead (*9*).

In the study area in southeastern Sweden, nickel-cadmium batteries have been produced since 1910 and lead batteries since 1942. Environmental cadmium and lead pollution from these plants has been substantial in the past (*14,15*). The total cadmium emissions have been calculated to be 8 tons into the air and 32 tons into water. The lead emission was mainly to air and was approximately 240 tons (*14*). One plant was closed in 1974, but the other is still operating. Occupational exposure to cadmium and lead was high during the first decades of plant operation, but has gradually decreased since the 1960s (*16,17*).

The aim of this study was to investigate the relationship between cadmium and lead in blood and bone mineral density (BMD) and tubular proteinuria.

Methods

This study is part of the OSCAR (Osteoporosis—cadmium as a risk factor) study, performed in the southeastern part of Sweden in two communities with environmental cadmium and lead pollution (*2,3*). A total of 1,465 subjects, ages 16 to 80, who had resided near the battery plant for at least 5 years between 1910 and 1992, were asked to participate, and 904 of them (62%) agreed to do so.

Several workers with previous or current occupational exposure from the two battery plants in the study area were also included. Out of 242 occupationally exposed workers, 117 (48%) agreed to participate in the examinations.

Thus, 1,021 individuals (60%) agreed to take part in the study and gave their informed consent to the investigation. Among the nonparticipants, a telephone survey of a random sample including 5% of the nonparticipants gave no indication that they differed from the examined group in a systematic way with regard to age, sex, or morbidity.

Each study subject received a questionnaire including questions regarding employment, residence, smoking, and food habits, as well as medical history, especially regarding kidney diseases and diseases related to osteoporosis. Specially trained nurses collected urine and blood samples and measured bone mineral density (BMD), height, and weight.

The presence of cadmium and lead in blood was determined by inductively coupled plasma mass spectrometry (ICP-MS). A quadropole spectrometer (VG PQ2+; Fisons Elemental, Winsford, Cheshire, UK) equipped with an autosampler (Gilson 222; Gilson, Villiers, France) was used. We used commercial reference samples to check the method accuracy.

We used urinary protein HC (human complex-forming glycoprotein, formerly called α_1-microglobulin) to detect early renal damage using single radial immunodiffusion for the determinations. The sensitivity of the method was 1.7 mg/L, and its total analytic imprecision (intra-assay and interassay) was 6% (*18*). The analyses were made at the Department of Clinical Chemistry at Lund

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University Hospital. Morning urine was voided in acid-washed polyethylene bottles and stored frozen (–20°C) until transfer to Lund University Hospital. At the laboratory, the sample was thawed and 10 mL urine was poured into a polypropylene tube. Subsamples for the determination of protein HC were pipetted from the sampling bottle into separate tubes and freeze stored until analysis. A preservative solution was added to the subsample for protein HC determination according to Tencer et al. (*19*). Protein HC was then adjusted to urinary creatinine to account for differences in dilution of the urine. Creatinine was measured using an enzymatic colorimetic method using a Hitachi Modular-P (Roche Diagnostics, Mannheim, Germany).

The cut-off points used for tubular proteinuria were 0.8 mg protein HC/mmol creatinine for men and 0.6 mg/mmole for women, which reflects the upper 95% limit in a Swedish reference population (*18*).

We measured bone mineral density (BMD) in the forearm, with an ambulant instrument (Osteometer DTX-200; Meditech A/S, Rødovre, Denmark), using dual energy X-ray absorptiometry (DXA), which is commonly used to evaluate BMD (*20*). We measured the nondominant arm with the patient in a supine position. We measured the BMD in the distal site in the forearm, which includes both the radius and the ulna from the 8-mm point (point where the radius and ulna are separated by 8 mm) and 24 mm proximally. The distal site contains 10–20% trabecular bone (*21*). We checked the internal variation by daily calibration using a phantom. We compared the measured BMD to a reference population furnished by the instrument supplier (Osteometer; Meditech). The reference population did not have any previous or present diseases known to influence calcium metabolism. No restrictions were made on smoking or other lifestyle habits. The ambulant instrument was used and validated in a previous study (*22*).

The degree of osteoporosis can be assessed by computing an age- and sex-standardized *z*-score (*23*). A common definition of low bone mineral density is *z*-score < –1 (*24*), which indicates one standard deviation below a sex- and age-standardized mean, which is used in the present study.

Variables with a skewed distribution were log transformed (log e) to achieve normal distribution when appropriate.

Multiple regression was used for the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were computed using logistic regression. All the statistical analyses were performed using the STATA 7.0 software (Stata Corp., College Station, TX, USA).

Results

Characteristics of the study population regarding sex, age, blood cadmium, blood lead, urinary excretion of protein HC, BMD, and smoking are presented in Table 1. The smokers had been smoking regularly for at least 1 year.

Table 2 shows the regression coefficients for the independent variables age, blood cadmium, blood lead, and smoking, with log-transformed protein HC as the dependent variable. There was a strong positive correlation between blood cadmium and age and protein HC. No similar effect was seen for blood lead. The results changed only marginally when analyzing blood cadmium and blood lead separately or when smoking was excluded. When the analyses were restricted to environmentally exposed persons, the results remained essentially the same.

Another way to examine the relation is to look at the dose–response relationship between blood cadmium and tubular proteinuria. A total of 171 people (128 environmentally and 43 occupationally exposed) had tubular proteinuria, using the above-mentioned cut off points. Figure 1 shows the odds ratios (with 95% CIs) for tubular proteinuria for different blood cadmium groups in the environmentally exposed group, after adjustment for age, sex, and smoking. The cut-off level for the lowest dose group was set at 5 nmol/L, and this group was used as the reference group (n = 658). The remaining subjects were divided into four groups of similar size (n = 84, 93, 80, 94). This produced cut-off-points for the different groups of 5, 7, 10, and 15 nmol/L. Excess risks for tubular proteinuria were found for all the groups exceeding 7 nmol cadmium/L blood.

As shown in earlier published data (*2*), BMD decreases more rapidly after 55–60 years of age in both men and women. The analyses of BMD thus focused on the older age group (> 60 years). In Table 3, a multiple linear regression is shown for the subgroup older than 60 years, with distal BMD as the dependent variable and age, weight, blood cadmium, blood lead, and smoking as independent variables. In both the whole group and the older subgroup there was a negative correlation between age and BMD and a positive correlation between weight and BMD. There was a negative correlation between cadmium dose, expressed as blood cadmium, for both men and women in the older age group—significant for women and close to significant for men. In contrast, we observed no significant trend for lead. In the whole group (all ages), no significant correlations could be found among blood cadmium, lead, and BMD. Smoking did not alter the analyses in a major way. The results only changed marginally if blood cadmium and blood lead were examined in separate analyses.

We conducted dose–response relationships for the bone effects in a similar way as for the renal effects. Table 4 shows the odds ratios (with 95% CIs) for low bone mineral density (*z*-score < –1) for three blood cadmium groups for people over 60 years of age, adjusted for weight and smoking. The *z*-score includes adjustment for age and sex as described above. The cut-off level for the lowest dose group was set at 5 nmol/L as above. The remaining subjects were divided into two groups of similar size (n = 177, 174). This produced cut-off points for the different groups of 5 and 10 nmol/L. Statistically significant differences were seen at blood cadmium levels > 5 nmol/L, and in the group with blood cadmium > 10 nmol/l the OR was 2.9 (95% CI = 1.4–5.8).

Table 1. Characteristics of the 1,021 individuals examined in the study.

Characteristics	Men (n = 479) Mean (10th, 90th percentiles)	Women (n = 542) Mean (10th, 90th percentiles)
Age	54 (range 18–81)	52 (range 16–81)
Blood Cd (nmol/L)[a]	7.6 (1.3, 17)	5.5 (1.5, 12)
Blood Pb (µmol/L)[b]	0.16 (0.08, 0.25)	0.11 (0.05, 0.17)
Urinary protein HC[c] (mg/mmol creatinine)	0.67 (0.16, 1.2)	0.46 (0.15, 0.8)
Distal bone mineral density (g/cm^2)	0.56 (0.46, 0.67)	0.44 (0.32, 0.54)
Smokers[d] (% former or current)	53	43

[a]Missing analyses for 5 men, 7 women. [b]Missing analyses for 6 men, 7 women. [c]Missing analyses for 9 men, 9 women. [d]Missing records for 3 men, 8 women.

Table 2. Multiple linear regression analysis for log transformed protein HC (mg/mmol creatinine) as a function of age, blood-cadmium, blood-lead, and smoking.

Characteristics	Men[a] (n = 460) Regression coefficient	95% CI	Women[b] (n = 521) Regression coefficient	95% CI
Age (years)	0.023	0.019–0.028	0.017	0.013–0.020
Blood Cd (nmol/L)	0.016	0.0099–0.023	0.015	0.0049–0.025
Blood Pb (µmol/L)	0.015	–0.80–0.83	–0.19	–0.99–0.60
Smoking (never or former/current)	–0.042	–0.18–0.096	0.028	–0.090–0.15

[a]R^2 = 0.26. [b]R^2 = 0.17.

Discussion

Our results show that there is a relationship between blood cadmium and tubular proteinuria and low bone mineral density. We found no similar associations for lead. The relationship between cadmium and tubular proteinuria is strong, even when the occupationally exposed participants are excluded. The subgroup with the highest cadmium levels had a 4-fold increased risk of having tubular proteinuria compared to the subgroup with the lowest blood cadmium levels. In the older age group (age > 60), the risk of low bone mineral density (*z*-score < –1) for the subgroup with the highest blood cadmium levels was almost three times that of the group with lowest blood cadmium levels.

It is difficult to find a perfect dose estimate for cadmium and lead, as with many other toxic agents. The dose estimate most often used for cadmium is urinary cadmium. However, renal damage may lead to a higher excretion of cadmium, as has been shown both in animal (*1,5*) and in human studies (*1,6,25,26*). It has been shown that blood cadmium can be a better dose estimate when tubular proteinuria is present (*27*). Examination of cadmium-exposed workers more than 15 years after the cessation of exposure showed a stronger association between blood cadmium and tubular proteinuria than between urinary cadmium and tubular proteinuria (*27*).

During high cadmium exposure, for example through occupational exposure, the cadmium concentration in blood increases relatively rapidly. After some months, cadmium in blood reaches a concentration that corresponds to the intensity of the exposure. If the exposure stops, the blood cadmium concentration decreases fairly rapidly, with an initial half-time of 2–3 months (*4,7*). However, cadmium accumulated in the body will influence the blood cadmium concentration. Therefore, after exposure ceases, the concentration in blood will not decrease to the preexposure level. Thus, cadmium in blood may serve as a good estimate of the accumulated body burden of cadmium.

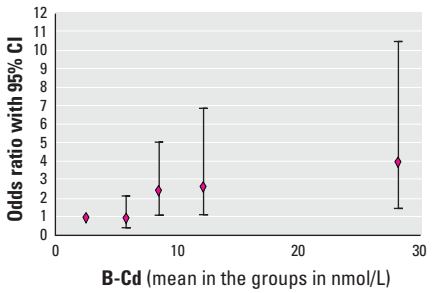

Figure 1. Odds ratios (95% CIs) for prevalence of tubular proteinuria related to blood cadmium (B-Cd) adjusted for age, sex, and smoking for the environmentally exposed group.

Also, in the general population, blood cadmium is influenced largely by the body burden of cadmium. One study on the influence on blood cadmium concentrations from various dietary factors showed no significant association between cadmium concentrations in blood and duplicate diets, while body burden, measured as urinary cadmium and S-ferritin (measure of body iron stores) were the main determining factors for blood cadmium (*28*). A study of environmentally exposed women in Japan also showed that blood cadmium correlated closely with urinary cadmium. Both blood and urinary cadmium correlated in this study with cadmium in food duplicates (copies of the food eaten by participants during the study) (*29*).

In nonsmoking, nonoccupationally exposed individuals in Sweden, the blood cadmium levels are usually between 0.9 and 7 nmol Cd/L, but in smokers the concentrations are often considerably higher (*30*). A Swedish study on an elderly population with a mean age of 87 years showed blood cadmium concentrations of 3.9 nmol/L in nonsmokers and 7.5 nmol/L in current smokers (*31*). A Japanese study on adult women in an area not defined as cadmium polluted showed mean cadmium levels in blood of 18.9 nmol/L (*32*). The mean blood cadmium levels in this study (7.6 nmol/L for men and 5.5 nmol/L for women) are in the upper normal limit of the general Swedish population, but lower than in Japan. It is important to remember that it is not possible to directly compare the blood levels in the present study with other groups with another exposure history. Most occupationally exposed and many of the environmentally exposed people in the current study had a much more pronounced exposure earlier when the battery plant still was operating. It is difficult to estimate which blood cadmium levels they had, for example, 30 years ago, although most probably they were higher. Another problem is that the prevalence, rather than the incidence, of tubular proteinuria and low BMD is being analyzed. It is not possible to say how high the exposure was at the time when the tubular proteinuria or the low BMD appeared.

In a Belgian study (*33*) on environmentally cadmium-exposed individuals, there was a negative correlation between urinary cadmium and forearm bone density in postmenopausal women. The results from the present study are in agreement with the Belgian report, with an effect especially in older people. In our earlier report from project OSCAR, using urinary cadmium as the dose estimate, the effect on the bone mineral density was more pronounced among men than women (*2*). This is in contrast to the present study where the effect is slightly more pronounced in women. However, it is not only the dose estimate that differs between the two studies; in the previous report an additional 41 occupationally highly exposed men and 2 women were included. These subjects were excluded from the present study because data were missing on blood cadmium and lead.

The effect of cadmium on bone mineral density is much more pronounced in older people (> 60 years) in the present study. This may reflect that the bone is more sensitive to cadmium as the bone ages. Another possible explanation is that it takes a couple of decades for cadmium to affect the bone. The infamous itai-itai disease in Japan, characterized by severe osteoporosis and osteomalacia, was most likely caused by cadmium and was found almost exclusively in older women (*1*).

In contrast to our findings on cadmium, we found no associations between blood lead and tubular proteinuria measured as protein HC excretion. The mean blood lead levels in

Table 3. Multiple linear regression analysis of BMD for the subgroup ages 60 years and older, as a function of age, weight, blood cadmium, blood lead, and smoking.

Characteristics	Men (n = 172)[a] Regression coefficient	95% CI	Women (n = 176)[b] Regression coefficient	95% CI
Age (years)	−0.0035	−0.0058–−0.0013	−0.0055	−0.0074–−0.0035
Weight (kg)	0.0022	0.0011–0.0032	0.0026	0.0017–0.0035
Blood Cd (nmol/L)	−0.00044	−0.0012–0.00035	−0.0030	−0.0054–−0.00066
Blood Pb (μmol/L)	−0.048	−0.20–0.10	0.078	−0.057–0.21
Smoking (never or former/current)	−0.020	−0.044–0.0035	0.019	−0.0077–0.045

[a] R^2 = 0.21. [b] R^2 = 0.28.

Table 4. Logistic regression model for low BMD (*z*-score < –1) including blood cadmium and smoking as categoric variables and weight as a continuous variable, for the subgroup older than 60 years.

Variable	OR	95% CI
Blood Cd < 5 nmol/L (mean 2.5)	1	—
Blood Cd ≥ 5 nmol/L and <10 nmol/L (mean 7.2)	2.0	1.1–3.9
Blood Cd ≥ 10 nmol/L (mean 21)	2.9	1.4–5.8
Smoking	0.82	0.46–1.5
Weight	0.96	0.94–0.98

our study were 0.16 µmol/L for men (range 0.08, 0.25) and 0.11 µmol/L for women (range 0.05–0.17). The levels that appeared to be the threshold for proximal tubular injury in both animal and human studies have been around 3 µmol/L (*11*). In concordance with the present results, other studies with lower lead blood levels have shown negative relations between blood lead kidney function (*26*).

Neither could we find any associations between lead and distal forearm bone mineral density. Different experimental and some human studies have shown that lead also may affect the bone. Studies on children have shown negative correlations between lead in blood and the levels of 1,25-dihydroxyvitamin-D (*34,35*). Experimental studies have shown different possible mechanisms on how lead may affect bone (*13*). It is possible that bone effects from lead exposure can occur at higher levels than in the present study.

Lead is often and most easily measured in blood, and it is a commonly used indicator of the total body burden (*9*). However, the half-life of lead in blood is short, about 36 days (*9*), so it typically represents mostly, but not only, recent exposure. Lead in blood is derived from levels in the environment and from lead stored in tissues, mostly bone, that reenters the blood. Maybe the results would have been different if the total body burden could have been better measured. Methods for detecting low lead levels in bone with *in vivo* X-ray fluorescence are now available (*36,37*), but are not easily accessible.

Thus, this report in combination with our earlier studies (*2,3*) show that cadmium exposure is related to early renal and bone effects regardless whether urinary or blood cadmium is used for dose estimation. The possible effect of tubular damage on the excretion of cadmium does not appear to confound these findings. Lead does not seem to be a confounder.

It is still debated whether early renal effects such as tubular proteinuria have any clinical effects. However, a newly published study from the area where this study was performed shows that the age-standardized rate ratio for end stage renal disease increased from 1.4 in the low-exposure group to 1.9 and 2.3 in the moderate- and high-exposure groups, respectively (*15*).

To summarize, we found a relationship between low blood cadmium and tubular proteinuria and low bone mineral density. These associations may be caused by higher cadmium exposure in the past. We found no such associations for blood lead. This study strengthens previous evidence that environmental cadmium exposure may affect both BMD and kidney function.

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