Cadmium may be a risk factor for osteoporosis

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Abstract
Objectives—The primary study aim was to examine the possible role of cadmium as a risk factor for osteoporosis by determining the bone mineral density (BMD) in workers previously exposed to cadmium. A second objective was to validate the BMD data obtained with a movable instrument.
Methods—43 workers who were exposed to cadmium for ≤5 years before 1978 were studied. Cadmium in blood (B-Cd) and urine (U-Cd) were used as dose estimates. The BMD was assessed in the forearm, the spine, and the hip (neck and trochanter) with a dual energy *x* ray absorptiometry (DXA) instrument. Age and sex matched reference populations were used to compute Z scores, commonly used to assess osteoporosis.
Results—The mean forearm Z score was -0.60 (95% confidence interval (95% CI) −1.08 to −0.12) in the group exposed to cadmium. The mean Z score for the spine was - 0.47 (95% CI −0.92 to −0.03), for the hip neck −0.40 (95 % CI −0.75 to −0.05), and for the hip trochanter −0.22 (95 % CI −0.52 to −0.07). The decrease in forearm BMD was correlated with age (p= 0.002) and B-Cd (p= 0.040). No such correlations were found for the other sites. Workers with tubular proteinuria had a lower forearm BMD (p= 0.029) and a lower Z score (p= 0.072) than workers without tubular proteinuria.
Conclusions—There was a suggested dose-effect relation between cadmium dose and bone mineral density. Furthermore, there was a dose-response relation between cadmium dose and osteoporosis. Cadmium may be a risk factor for the development of osteoporosis at lower doses than previously anticipated.
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High exposure to cadmium was the cause of the feared itai-itai (ouch-ouch) disease in Japan, where cadmium contaminated rice was ingested by the local farmers leading to osteoporosis and osteomalacia.[1] [2] In recent years, cross sectional examinations of people living in areas of Japan polluted by cadmium have shown evidence of lowered bone calcium and reduced concentrations of kidney activated vitamin D.[3–5] A few studies have shown a pattern similar to that of patients with itai-itai among workers exposed to high concentrations of cadmium.[2] [6] Animal experiments have shown that cadmium in much lower doses may cause osteoporosis.[7]

To our knowledge there are no studies indicating an association between environmental cadmium and decreased bone mineral density (BMD) outside the areas in Japan polluted by cadmium. The main objective of the present study was to investigate the relation between cadmium dose and BMD in workers previously exposed to cadmium. A second objective was to evaluate a mobile instrument, which was used to assess BMD in a larger population based study of cadmium exposure and osteoporosis.

Subjects and methods

SUBJECTS
In 1993, 46 workers exposed to cadmium at a plant that manufactured heat exchangers and coolers took part in an investigation to study the glomerular filtration rate[8] and the association between blood cadmium as a dose estimate and different markers of tubular proteinuria (ß$_2$-microglobulin, protein HC (α$_1$-microglobulin) and N-acetyl-β-D-glucosaminidase (NAG)).[9] The workers had been exposed to cadmium for ≤5 years before 1978, when soldering material containing cadmium was abandoned. We invited these 46 workers to take part in the present investigation of the skeleton, and 43 of them (41 men and two women) agreed to participate.

METHODS
Cadmium in blood (B-Cd) was determined with inductively coupled plasma mass spectrometry (ICP-MS, Fisons VG Plasmaquad PQ2) at the Department of Occupational and Environmental Medicine at the University
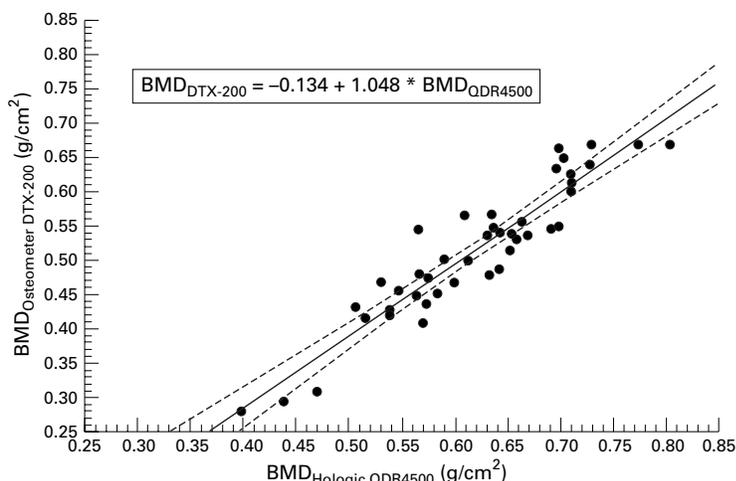

Figure 1   Forearm bone mineral density (BMD) in solderers exposed to cadmium, measured by a movable instrument (Osteometer DTX-200) as a function of forearm BMD measured by a hospital based instrument (Hologic QDR 4500).

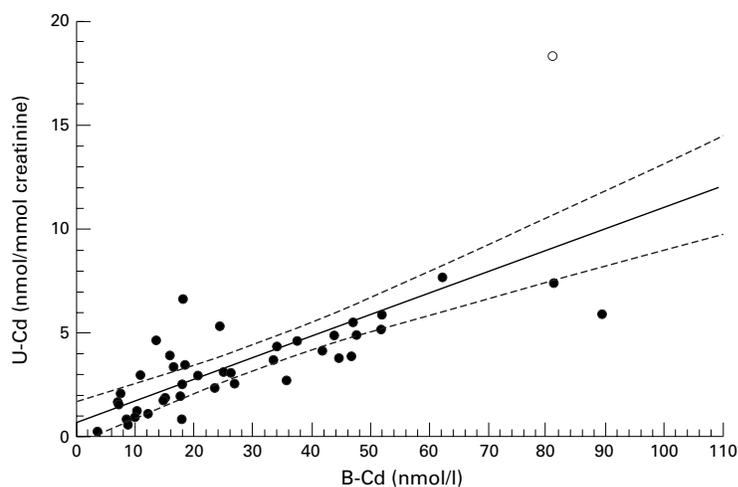$$BMD_{DTX-200} = -0.134 + 1.048 * BMD_{QDR4500}$$

Figure 2   Urinary cadmium measured in 1993 as a function of B-Cd measured in 1996.
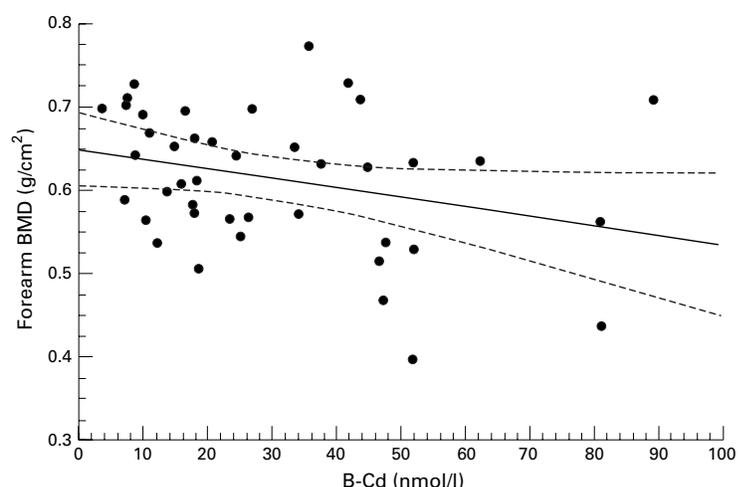

Figure 3   Forearm bone mineral density as a function of B-Cd in workers exposed to cadmium.
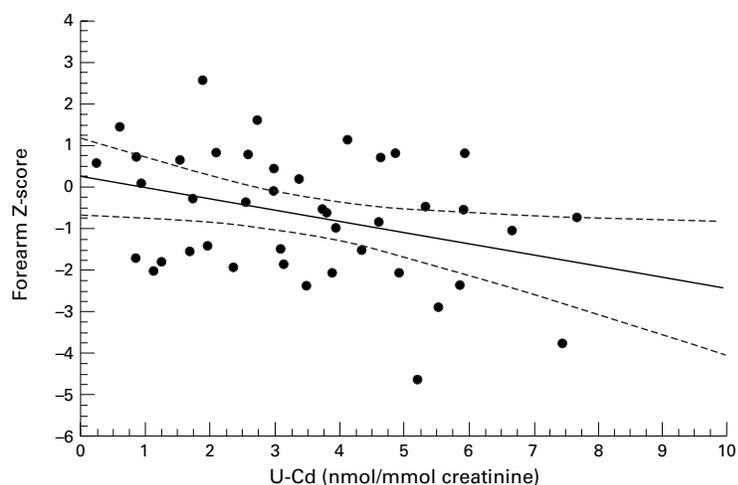

Figure 4   Forearm Z score as a function of U-Cd in workers exposed to cadmium.

Hospital in Lund. The samples (0.50 ml blood) were diluted 10-fold with a solution containing EDTA (0.5 g/l), Triton-X100 (0.5 g/l) and ammonia (5 ml/l) in Millipore water, and 100 µl of an internal standard solution, containing 50 ng indium, was added. Each sample was

prepared in duplicate. The sample solutions were introduced into a spray chamber in a segmented flow mode, with the diluent as a carrier and rinsing fluid. The detection limit of this method was 0.01–0.04 µg Cd/l. The precision, calculated as the coefficient of variation for the duplicate measurements, was 5%. The accuracy was checked by including commercial reference samples (Seronorm, Nycomed, Oslo, Norway) of lyophilised whole blood and urine in each analytical series.

Cadmium in urine (U-Cd) was measured in 1984 and 1993 at the Department of Occupational Medicine at Linköping University Hospital.[8] [9]

Bone mineral density was measured with two different instruments. Forearm BMD was measured with an ambulant instrument (Osteometer DTX-200), whereas BMD of the forearm, lumbar spine, and hip (neck and trochanter) was measured with a hospital based instrument (Hologic QDR 4500). Both instruments use the dual energy *x* ray absorptiometry (DXA) technique. The non-dominant arm was measured with the patient in a supine position. The internal variation was checked by daily calibration with a phantom. The BMD assessed by the stationary instrument was compared with a reference material provided by the instrument supplier[10] and to a local reference material (Löfman O, personal communication). The BMD assessed by the movable instrument was compared with a reference population furnished by the instrument supplier, based on measurements performed on normal Danes, aged 20–88 years, who were healthy volunteers. Subjects included in 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.

Age and sex standardised Z score values were computed according to the formula:

Z score = $(X_u - X_m)/SD$

where X_u = measured bone density, X_m = group mean for the same age group, SD = standard deviation in the reference population.

A common definition of osteoporosis, Z score <−2 was used.[11] Data on α_1-microglobulin and β_2-microglobulin from 1993 were used to assess the degree of renal tubular dysfunction. Data on the glomerular filtration rate (GFR) from 1993 were used to estimate the degree of glomerular dysfunction.

STATISTICAL METHODS
Data were analysed with standard statistical methods, *t* test for the comparison of means, and multiple regression for the multivariate analyses.

UNITS
Cadmium in blood is given in nmol/l (1 µg/l = 8.9 nmol/l) and cadmium in urine is given in nmol/mmol creatinine. β_2-Microglobulin in urine is shown as µg/mmol creatinine (1 µg/g creatinine = 0.112 µg/mmol creatinine).

Table 1   Determinants of forearm bone mineral density in workers exposed to cadmium, with blood cadmium (B-Cd) as a dose estimate of exposure to cadmium

Regression variable	Coefficient	p Value
Age	−0.005	0.002
B-Cd	−0.002	0.040
Sex	−0.041	0.535
Weight	0.001	0.168
Smoking	−0.010	0.374
β_2-Microglobulin (1993)	0.000008	0.297
α_1-Microglobulin (1993)	0.0006	0.266
Glomerular filtration rate (1993)	−0.0010	0.196

Table 2   Determinants of forearm bone mineral density in workers exposed to cadmium, with urinary cadmium (U-Cd) as a dose estimate of exposure to cadmium

Regression variable	Coefficient	p Value
Age	−0.005	0.004
U-Cd	−0.02	0.052
Sex	−0.03	0.699
Weight	0.002	0.158
Smoking	−0.09	0.476
β_2-Microglobulin (1993)	−0.000002	0.927
α_1-Microglobulin (1993)	0.0007	0.278
Glomerular filtration rate (1993)	−0.0006	0.417

Results

There was a good correlation between forearm BMD measured with the DTX 200 and the Hologic QDR 4500 (fig 1). As the hospital based instrument was considered superior, we used the measurements obtained from the Hologic QDR 4500 for the further analyses.

There was a good correlation between B-Cd estimated in 1996 and the 1993 estimates of U-Cd (fig 2). One worker (marked with an unfilled circle, fig 2) had an extremely pronounced tubular proteinuria and was excluded from the analyses in which U-Cd was used as the dose estimate.

The mean forearm Z score was significantly decreased in the group exposed to cadmium. The mean Z score value was −0.60 (95 % confidence interval (95% CI) −1.08 to −0.12). The mean Z score for the spine was −0.47 (95% CI −0.92 to −0.03), for the hip neck −0.40 (95 % CI −0.75 to −0.05) and for the hip trochanter −0.22 (95 % CI −0.52 to −0.07).

A dose-effect relation was suggested between B-Cd and forearm BMD (fig 3). No dose-effect relations were found for the spine or hip. A dose-effect relation was also suggested between U-Cd and Z score (fig 4). To account for the influence of age, sex, and other known or suspected risk factors (weight, smoking, and renal dysfunction) on BMD, a multiple

Table 3   Dose-response relation between blood cadmium (B-Cd) and prevalence of osteoporosis (Z score <−2) in workers exposed to cadmium

B-Cd, group (nmol/l)	B-Cd, mean (nmol/l)	Cumulative exposure (mg/m³.y)	Total subjects (n)	Subjects with osteoporosis (Z score <−2.0)	Prevalence (%)
<40	18	2.0	30	1	3.3
≥40	57	4.7	13	6	46.2

Table 4   Dose-response relation between urinary cadmium (U-Cd) and prevalence of osteoporosis (Z score <−2) in workers exposed to cadmium

U-Cd group (nmol/mmol creatinine)	U-Cd mean (nmol/mmol creatinine)	Total subjects (n)	Subjects with osteoporosis (Z score<−2.0)	Prevalence (%)
<5	2.7	33	3	9.1
≥5	7.4	10	4	40.0

regression analysis was performed including age and other relevant variables. Tables 1 and 2 show the results.

We then divided the group of workers into two subgroups according to their cadmium dose. There was a suggested dose-response relation between B-Cd and osteoporosis (defined as Z score < −2.0, table 3. Note that the Z score is adjusted for age and sex. Further corrections for age should thus not be made). Table 4 shows a similar relation between U-Cd and osteoporosis.

The subgroup with tubular proteinuria (defined as α_1-microglobulin > 1 mg/mmol creatinine) had a lower Z score than the subgroup without tubular proteinuria (p=0.072).

Discussion

We have previously shown that B-Cd is a good dose estimate several years after the end of exposure.[9] When tubular damage has occurred, B-Cd is a better dose estimate than U-Cd, as the kidney damage leads to a higher excretion of cadmium in urine. The current concentrations of blood cadmium were considerably lower than those found shortly after the excessive workroom exposure to cadmium at the end of the 1970s.[12] Likewise, urinary excretion of cadmium has decreased, on average, by at least 57% since exposure ended.[9] Thus, recently measured B-Cd values cannot readily be used for comparisons with other groups with current exposure to cadmium, or those having another exposure history. There is, however, a close linear correlation between the recent B-Cd data (1996) and previous U-Cd data (1984 and 1993). A B-Cd in 1996 of about 40 nmol/l corresponds to a U-Cd excretion around 5 nmol /mmol creatinine in 1993 (fig 2).

Two different instruments were used to measure BMD, a movable instrument (Osteometer DTX-200), and a stationary hospital based instrument (Hologic QDR 4500). There are several different techniques available for assessing BMD, the most common being based on *x* ray films. Present measuring techniques based on *x* ray films have a precision in vivo of 1.5% or better. Both the stationary hospital based instrument and the movable one are claimed to have a precision of <1%. The movable instrument is currently being used in a large population based study on environmental exposures and the risk for osteoporosis. Thus, it was of great importance to validate the movable instrument against an established hospital based one. The BMD values resulting from the DTX-200 measurements were 15% lower than the values obtained with the Hologic QDR 4500, which may be due to slightly different measuring positions. The regression coefficient (1.048) indicates, however, a very good agreement between the instruments and it was concluded that the DTX 200 showed valid forearm BMD data and can be used with confidence in other studies.

Since the discovery of itai-itai disease in the 1950s it has been recognised that very high cadmium exposure can lead to osteoporosis or

osteomalacia. Only a few cases of bone disorders have been reported outside the cadmium polluted areas in Japan. Japanese studies show decreased BMD at B-Cd concentrations of the order of 100 nmol/l.[13]

Animal experiments have shown that bone resorption due to cadmium exposure can occur at B-Cd concentrations similar to those reported for people occupationally exposed to cadmium and for people who smoke cigarettes (27–80 nmol/l). Moreover, these bone effects may occur early before the development of tubular damage.[7]

The present findings indicated a decreased BMD in workers exposed to cadmium at lower concentrations of B-Cd (mean 29.3 , range 3.5–89.4 nmol/l) than previously noted in humans, but in accordance with the experimental findings in animals.

There was a suggested dose-effect relation between B-Cd and BMD, as well as between U-Cd and BMD, significant at the 95% level, when other risk factors were included in the regression model. As expected, age was the most important determinant of BMD. Weight had a positive, but non-significant, regression coefficient in accordance with previous findings.[14]

The discrepancy found between different parts of the skeleton (low BMD in the forearm, normal in spine and hip) is not unusual. Although post-menopausal osteoporosis and cortisone induced osteoporosis initially dominate in trabecular bone, bone loss due to hyperparathyroidism and senile osteoporosis, for example, is most marked in the cortical bone of the forearm. It should be noted that forearm BMD is a good predictor of fractures, regardless of location.

We defined a subgroup of highly exposed people, with a cut off point for B-Cd of 40 nmol/l, which is above the 90th percentile among non-occupationally exposed smokers in Sweden (30 nmol/l),[15] but considerably below the B-Cd concentrations found in patients with itai-itai (100–400 nmol/l).[13] With U-Cd as the dose estimate, it should be noted that a 1993 U-Cd value of 5 nmol/mmol creatinine corresponded roughly to a 1984 U-Cd value of 10 nmol/mmol creatinine, which is the health based limit of the World Health Organisation. Thus, regardless of whether cadmium in blood or urine was used for estimating the cadmium dose, signs of osteoporosis occurred at lower cadmium concentrations than previously anticipated.

Furthermore, the definition of osteoporosis is debated and various measures have been used. Although osteoporosis in women has been defined as BMD >2.5 SD below the normal mean of a young adult healthy woman,[16] there is no corresponding definition for men as yet. A BMD of one SD below the mean for a particular age is commonly applied (Z score < -1.0).[17] Another, more strict definition of osteoporosis (Z score < -2) has also been suggested.[11] This definition was chosen in the present study to characterise cases with marked osteoporosis. Table 2 shows that there was a suggested dose-response relation between dose of cadmium and the prevalence of pronounced osteoporosis.

Other potential risk factors for osteoporosis include nutritional and lifestyle factors, decreased oestrogen concentrations, and smoking.[18] Our study did not find any significant associations between smoking and BMD. Oestrogen concentrations were not included, as only two of the workers were women and both were premenopausal (39 and 40 years old). Nutritional factors were not investigated, but should not differ significantly from the reference population.

Few environmental causes of osteoporosis have been studied and apart from cadmium, other metals such as lead and aluminium have been discussed.[19] The present study group were not known to be exposed to other metals to any extent.

In Japan, examination of people environmentally exposed to cadmium have shown an association between renal tubular dysfunction (β_2-microglobulinuria) and decreased BMD in women but not in men.[3] β_2-Microglobulin was not measured in the present study, but as cadmium induced tubular lesions are irreversible we used the 1993 data.[8] There was no significant association between urinary β_2-microglobulin and BMD in this predominantly male group, which accords with the Japanese findings. The subgroup with tubular proteinuria (α_1-microglobulinuria) had a lower BMD than the group without tubular proteinuria, supporting the theory that cadmium may affect the bone mineralisation through the kidneys.

One possible link between cadmium accumulation in the kidney and bone demineralisation may be through a decreased renal activation of vitamin D to calcitriol. Reports from two of the areas of Japan polluted by cadmium show significant associations between renal damage induced by cadmium in the form of β_2-microglobulinuria, or increased serum creatinine, and lowered plasma concentrations of calcitriol.[4 5]

Conclusion

There was a suggested dose-effect relation between cadmium dose and bone mineral density. Furthermore, there was a suggested dose-response relation between cadmium dose and osteoporosis. Although the present study population is small, the findings indicate that cadmium may cause bone demineralisation at a lower dose of cadmium than was previously anticipated.

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2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histmaine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med 1976*;**294**:687-90.

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