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Low level cadmium exposure, renal and bone effects - the OSCAR study

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Abstract

It is well known that high cadmium exposure causes renal damage, osteoporosis and osteomalacia, whereas the dose-response relationships at low-level exposure are less well established. WHO estimated (1992) that a urinary excretion of 10 nmol/mmol creatinine would constitute a 'critical limit' below which kidney damage would not occur. Later, Belgian and Swedish studies have shown signs of cadmium induced kidney dysfunction in the general population already at urinary cadmium levels around 2–3 nmol/mmol creatinine.

The Swedish OSCAR (OSteoporosis-CAdmium as a Risk factor) study comprised 1021 individuals, exposed to cadmium in the environment. Blood and urinary cadmium were used as dose estimates. Protein HC (α-1-microglobulin) was used as an indicator of renal tubular damage. Forearm bone mineral density (BMD) was assessed with DXA (dual energy x-ray absorptiometry) technique. The study showed that tubular proteinuria occurred at much lower levels of cadmium dose than previously known. A negative dose-effect relationship was found between cadmium dose and BMD for people at the age of 60 or older. In this age group, there was also a dose-response relationship, showing a three-fold increased risk of low BMD in the group with urinary cadmium over 3 nmol/mmol creatinine, as compared to the lowest dose group. There was also evidence of an increased risk of forearm fractures with increasing cadmium levels in the population 50 years of age or older.

The potential public health consequences of low level cadmium exposure should be recognized, and measures taken to reduce cadmium exposure to an absolute minimum.

Introduction

Lars Friberg reported already in the 1940's that adverse effects on bones and kidneys may occur in cadmium exposed workers (Friberg 1950). A few years later, Japanese investigators discovered the 'Itai-itai disease', characterised by renal disease, osteomalacia and osteoporosis, which was caused by cadmium contaminated rice (Hagino 1955).

Later, it was reported that Belgians living in cadmium contaminated areas, showed signs of tubular proteinuria, indicating that cadmium induced renal effects were not confined to the heavily polluted areas in Japan (Buchet *et al.* 1990). Animal and human studies during the 1980's and the early 1990's also suggested that cadmium may affect bone tissue at much lower levels than in the contaminated Japanese areas (Bhattacharyya *et al.* 1992; Staessen *et al.* 1991; Järup *et al.* 1998).

Production of nickel-cadmium batteries started in Fliseryd (south-eastern Sweden) in 1912. Most of the discharges from the factory were emitted to the river Emån (90%), and the rest to the ambient air. Total cadmium emissions from this process have been estimated to 3.6 tons to ambient air and 32 tons to the river water.

The main aim of the OSCAR (OSteoporosis - CAdmium as a Risk factor) study was to investigate the effects of low-level cadmium exposure on bone. Another aim was to further evaluate the kidney effects. In particular the study set out to explore the dose-effect and dose-response relationships between low-level cadmium dose, renal tubular damage and bone mineral density (BMD).

Table 1. Number of invited persons and participants

Group	Invited	Participated	%
Battery plant workers	242	117	48
Residents of Fliseryd	1259	768	61
Referents	206	136	66
Total	*1707*	*1021*	*60*

Subjects and methods

In order to obtain a wide range of cadmium exposure in our investigation, we enrolled occupationally exposed workers, environmentally exposed subjects from Fliseryd, and people from a town in the same area, but further away from the battery plants. A summary of the study participants is shown in Table 1 (Alfvén, 2002).

All participants had given informed consent, and the study was approved by the ethical committee at Karolinska Institutet.

A telephone survey of a random sample of 5% of the non-participants (both occupationally and environmentally exposed) was performed. It gave no indication that the non-participants differed from the examined group in a systematic way with regard to age, gender, or fracture incidence.

The participants received a mailed questionnaire and a specially prepared bottle for collection of morning urine. They handed in the questionnaire at a visit to the local health centre. At the same visit, urine and blood samples were collected by specially trained nurses, who also measured height, weight and BMD. Blood and urine were kept frozen until analysed. The questionnaire including questions on employment, places of residence, smoking and food habits as well as medical history, especially fractures and diseases related to osteoporosis and kidney diseases.

Subjects were classified as occupationally exposed if they had worked in either of the battery plants for at least one year. Smokers were classified into never smokers or into former or current smokers if they had smoked regularly for at least one year. An estimate of dietary calcium intake was calculated from the reported consumption of dairy products.

Only fractures that had occurred at age 20 or later were taken into account. Persons younger than 20 years were excluded from the fracture risk analyses. Fractures reported in the questionnaires were validated using X-Ray and medical records from the only hospital in the area, where fractures occurring in the region are treated. A random sample of 40 participants who had not reported any fractures was also checked against the medical records.

Cadmium in urine and cadmium and lead in blood were determined using inductively coupled plasma mass spectrometry (ICP-MS, Fisons VG Plasmaquad PQ2) at the Department of Occupational and Environmental Medicine at the University Hospital in Lund. The accuracy was checked by including commercial reference samples. Earlier measurements of blood and urinary cadmium of the workers at the battery plants had during the 1970's been performed at the Department of Hygiene at Karolinska Institutet, and later at an independent laboratory with quality controls fulfilling WHO standards (Järup and Elinder 1994). Adjustments for variation in urinary concentrations between individuals were made by dividing the urinary cadmium values by the creatinine concentrations.

Urine for determination of Protein HC was stored frozen (−20 °C) with a preservative solution, until analyses were conducted by the Department of Clinical Chemistry at the University Hospital in Lund, using single radial immunodiffusion. The cut-off levels for tubular proteinuria were 0.8 and 0.6 mg protein HC per mmol creatinine, for men and women respectively, representing the 95% limits in a reference population consisting of healthy adults from southern Sweden, 200 kilometres from the study area (Tencer *et al.* 1996).

Bone mineral density (g/cm^2) was measured in the non-dominant forearm (distal site) with the patient in a supine position using an ambulant instrument (Osteometer DTX-200). The internal variation was checked by daily calibration using a phantom.

Z-scores[1] were calculated in comparison to a reference population, consisting of 800 Danes, aged 20–88 years, who were healthy volunteers without any diseases known to influence calcium metabolism. For the classification of osteoporosis, we used a common definition of low bone mineral density (Z-score < -1) (Kanis *et al.* 1997).

Statistical methods

Variables with a skewed distribution were log transformed to achieve normal distribution when appropri-

[1] Z-Score = $(X_u - X_m)/SD$, where X_u = measured bone density, X_m = group mean for the same age group and SD = standard deviation in the reference population

Table 2. Dose effect relation between urinary cadmium and urinary protein HC for all the study subjects and for only the environmentally exposed, men and women, adjusted for age

	Total population		Environmentally exposed	
	Men[a]	Women[b]	Men[c]	Women[d]
	Regression Coefficient (95% CI)	Regression Coefficient (95% CI)	Regression Coefficient (95% CI)	Regression Coefficient (95% CI)
Age	0.0098 (0.00092, 0.019)	0.0074 (0.0043, 0.010)	0.0090 (0.0040, 0.014)	0.0047 (0.0012, 0.0081)
Urinary cadmium (nmol/mmol creatinine)	0.45 (0.37, 0.52)	0.11 (0.035, 0.19)	0.37 (0.045, 0.70)	0.40 (0.25, 0.54)

[a]$R^2 = 0.24$ [c]$R^2 = 0.078$
[b]$R^2 = 0.075$ [d]$R^2 = 0.11$

Table 3. Logistic regression model for low bone mineral density (Z-Score < -1), including urinary cadmium (nmol/mmol creatinine) as a categorical variable, and weight as continuous variables

Variable	Odds ratio	95% CI
U-Cd < 0.5	1	–
U-Cd $>= 0.5$ and < 3	1.12	0.81–1.56
U-Cd $>= 3$	3.2	1.72–5.9
Weight	0.931	0.918–0.947

ate. Multiple regression was used for the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were computed using logistic regression. The associations between cadmium and tubular proteinuria and the risk of forearm fracture were examined using Cox proportional hazards regression analyses. Current cadmium in urine and blood and lead in blood were used as proxies for the cadmium and lead dose, respectively, at the time prior to the fracture. The time at risk for a forearm fracture was defined as the follow-up period. The follow-up period ended with the first reported forearm fracture, or if no fracture occurred in 1997.

Results

A positive, statistically highly significant, linear relation was found between cadmium in urine and urinary protein HC after adjustment for age for both genders (Järup *et al.* 2000). Table 2 shows the regression coefficients for the independent variables age and U-Cd, with protein HC as the dependent variable with all study subjects included (Alfvén, 2002).

The dose response relationships (for elevated urinary protein HC) for the environmentally and occupationally exposed groups are shown in Figure 1 (Alfvén 2002).

When blood cadmium was used as an estimate of the cadmium dose, there was an equally strong positive correlation between cadmium and protein HC (Alfvén *et al.* 2002).

Bone mineral density was negatively associated with age. BMD decreased more rapidly after 55–60 years of age in both men and women (Alfvén *et al.* 2000). Therefore, we focused the analyses on the older age group (60 years and older). There was a clear dose-effect relationship between cadmium dose (cadmium in urine) and BMD for subjects aged 60 and over (Alfvén *et al.* 2000). We also analysed the dose-response relationships between urinary cadmium and low bone mineral density, using the cut-off point Z-score < -1 to define low bone mineral density. Table 3 shows a logistic regression model including urinary cadmium and weight (Alfvén 2002). There was a three times (OR= 3.2, 95% CI: 1.7–5.9) higher risk of low bone mineral density in the group having urinary cadmium levels over 3 nmol/mmol creatinine, compared with the lowest dose category.

The mean age for having a forearm fracture was 46 years (youngest 21, oldest 69) (Alfvén 2002). Medical records confirmed twenty-eight of 32 forearm

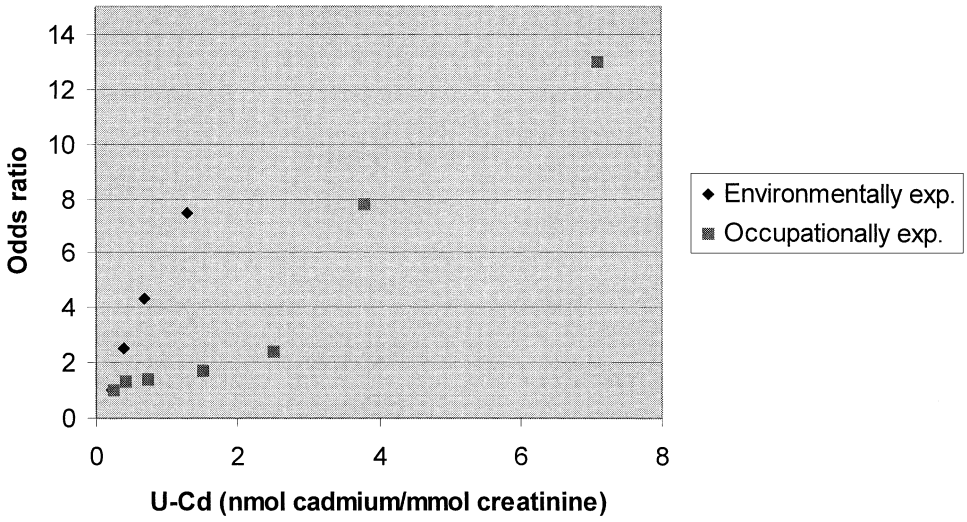

Fig. 1. Odds ratios for prevalence of tubular proteinuria related to urinary cadmium for the environmentally and occupationally exposed groups, adjusted for gender and age.

fractures that occurred after 50 years of age. For fractures occurring after the age of 50 years the adjusted hazard ratio for forearm fracture was 1.18 (95% C.I. 1.01, 1.37) per unit nmol cadmium/mmol creatinine. For forearm fractures before the age of 50, no associations were observed in relation to cadmium dose. Therefore, the cadmium related fracture hazard ratios for different levels of cadmium dose would not be constant over the follow-up time, as required in Cox regression analyses, without implementing a restriction on age at risk. For age at risk beyond age 50, the proportional hazard assumption was not violated. In this age group there was an increasing hazard ratio for forearm fractures with urinary cadmium levels, with a hazard ratio of 9 at the highest urinary cadmium level (6 nmol/mmol creatinine).

Simultaneous to the OSCAR study, further Belgian studies (PheeCad) were performed, showing similar excess fracture risks at low levels of cadmium exposure (Staessen *et al.* 1999).

Conclusions

Tubular proteinuria, an early sign of renal dysfunction occurred in cadmium-exposed people at lower levels than previously anticipated. A dose-effect relationship was found between cadmium dose and BMD for people aged 60 and older. In this age group, there was also a dose-response relationship, with a three-fold excess risk of low BMD in the highest compared to the lowest dose group.

There was evidence of an excess risk of forearm fractures associated with cadmium exposure, evidenced by the fracture hazard ratio, which increased with increasing cadmium levels in the population over 50 years of age. Evidence of renal tubular damage, in the form of elevated urine protein HC, was negatively related to BMD, and increased risk of forearm fractures, suggesting that the possible effect of cadmium on bone may be an indirect effect mediated by the kidneys.

The Swedish OSCAR study and the Belgian PheeCad study both suggest that also low level cadmium exposure may be a risk factor for osteoporotic fractures. Although these studies need further confirmation, the potential public health consequences should be recognized, and measures taken to reduce cadmium exposure to an absolute minimum.

References

Alfvén T. 2000 Bone and kidney effects from cadmium exposure - Dose effect and dose response relationships. Doctoral thesis, Karolinska institutet, Stockholm, Sweden.

Alfvén T, Elinder CG, Carlsson MD, Grubb A, Hellström L, Persson B, Pettersson C, Spång G, Schütz A, Järup L. 2000 Low level cadmium exposure and osteoporosis. *J Bone Mineral Res* **15**, 1579–1586.

Alfvén T, Järup L, Elinder CG. 2002 Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. *Environ Health Persp* **110**, 699–702.

Bhattacharyya MH, Sacco-Gibson NA, Peterson DP. 1992 Cadmium-induced bone loss: increased susceptibility in female beagles after ovariectomy. *IARC Sci Publ* **118**, 279–286.

Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F *et al.* 1990 Renal effects of cadmium body burden of the general population. *Lancet* **336**(8717), 699–702.

Friberg L. 1950 Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. A clinical and experimental study. Industrial Hygiene Department of the Swedish Public Health Institute, Department for occupational Medicine, Karolinska Hospital, Sweden.

Hagino N, Kono M. 1955 A study on the cause of Itai-itai-disease. Proc 17th Mtg Japanese Soc of Clinical Surgeons (in Japanese).

Järup L, Elinder CG. 1994 Dose-response relations between urinary cadmium and tubular proteinuria in cadmium-exposed workers. *Am J Ind Med* **26**(6), 759–769.

Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M. 1998 Health effects of cadmium exposure–a review of the literature and a risk estimate. *Scand J Work Environ Health* **24** Suppl 1, 1–51.

Järup L, Hellström L, Alfvén T, Carlsson MD, Grubb A, Persson B, Pettersson C, Spång G, Schütz A, Elinder C-G. 2000 Low level cadmium exposure and early kidney damage - the OSCAR study. *Occup Environ Med* **57**, 668–672.

Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. 1997 Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int* **7**(4), 390–406.

Staessen J, Amery A, Bernard A, Bruaux P, Buchet JP, Claeys F *et al.* 1991 Effects of exposure to cadmium on calcium metabolism: a population study. *British Journal of Industrial Medicine* **48**(10), 710–714.

Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J *et al.* 1999 Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. *Lancet* **353**(9159), 1140–1144.

Tencer J, Thysell H, Grubb A. 1996 Analysis of proteinuria: reference limits for urine excretion of albumin, protein HC, immunoglobulin G, kappa- and lambda-immunoreactivity, orosomucoid and alpha 1-antitrypsin. *Scand J Clin Lab Invest* **56**(8), 691–700.

World Health Organization. Cadmium Environmental Health Criteria 134. Geneva: WHO, 1992.