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Environmental cadmium exposure and forearm bone density

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Abstract

Environmental exposure to cadmium may give rise to osteomalacia combined with renal dysfunction, so called 'Itai-Itai disease', which was endemic in the heavily polluted area in Japan. The main focus of this study was to investigate whether environmental exposure to cadmium is associated with low bone mass in a population living near a smelter. A total of 790 persons (302 males and 488 females), who were all over 35 years old and resided in areas near a lead, zinc and cadmium smelter and in a control area in southeast China, completed a questionnaire, and bone mineral density was measured by SPA-4 single photon absorptiometry at the radius and ulna. Cadmium content of urine was determined by graphite-furnace atomic absorption spectrophotometry as a measure of dose. The present study shows that forearm bone densities were negatively correlated with urinary cadmium excretion ($p < 0.001$) and forearm bone density decreased linearly with age ($p < 0.001$) and urinary cadmium ($p < 0.01$), suggesting a dose-effect relationship between cadmium dose and bone mineral density. Based on the World Health Organization criteria, (bone mineral density < -2.5 SDs below the normal young adult), the prevalence of osteoporosis in women increased from 34.0% in the control area to 51.9% in the heavily polluted area ($p < 0.01$) among subjects over 50 years old, and the odds ratio value was 2.09 (95% CI: 1.08–4.03) for the highly polluted area compared with the control area. A striking observation in the study was a marked increase of the prevalence of fracture in the cadmium-polluted area in both sexes. It was concluded that environmental exposure to cadmium is associated with an increased loss of bone mineral density in both gender, leading to osteoporosis and increased risk of fractures, especially in the elderly and in females.

Introduction

It was reported that environmental exposure to cadmium may interfere with the metabolism of calcium, vitamin D, and collagen (Järup *et al.* 1998; Kjellström 1985), and may give rise to osteomalacia combined with renal dysfunction, so called 'Itai-Itai disease', which was considered to be the most severe form of chronic cadmium intoxication and was endemic in the heavily polluted mining area in Japan (Kjellström 1985). The clinical features include bone and kidney damage (Kjellström 1992), while pathological bone findings are a combination of osteomalacia and osteoporosis (Kjellström 1986).

Cadmium may have both direct and indirect effects on bone turnover, directly on osteoblast and osteoclast function, and indirectly via kidney dysfunction (Berglund *et al.* 2000). Cadmium is nephrotoxic and can interfere with vitamin D metabolism, and the perturbation of vitamin D metabolic pathway by cadmium may result in health effects such as osteoporosis and osteomalacia (Chalkley *et al.* 1998). Osteoporosis is a common metabolic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in risk of fracture (Consensus development conference 1993). It was pointed out that osteoporosis was also seen in itai-itai

disease patients and had been considered to be a more common bone effect of cadmium than osteomalacia. However, it is still disputed whether cadmium-induced bone effects can occur outside this area of Japan. Recently, a negative association between cadmium dose and bone mass has been found in both occupationally and environmentally exposed people at relatively low cadmium exposure (Alfvén *et al.* 2000; Staessen *et al.* 1999). But only a few new epidemiological studies were reported in the last decade.

The main focus of this previously reported study (Wang *et al.* 2003) was to investigate, using single-photon absorptiometry, whether environmental exposure to cadmium is associated with low bone mass in a population living near a smelter.

Materials and methods

Areas and Study population

A smelter is located in the South part of China. Lead and zinc are the main products in this smelter, which started production in 1961. It is estimated that about 100,000 tons of industrial waste water per year is discharged to a river in front of the factory. The residents of the polluted areas used the polluted river to irrigate their fields from 1961 to 1995. The rice is the main food for the residents in these areas.

The village near the smelter (half a kilometer away) was selected as highly polluted area based on an investigation in 1995, showing that in this village (Jiaoweibao), the average Cd concentration of rice produced in the residents own fields was 3.7 ± 1.8 mg/kg in polished rice. This was 18-fold higher than the state hygienic standard (0.2 mg/kg). From 1996, the residents of the highly polluted area stopped producing rice in these fields and started to eat commercial rice from non polluted areas. Another village (Nanbaixiang) with an average Cd concentration in 1995 of 0.51 ± 0.19 mg/kg in polished rice was selected as medium polluted area. It is situated 12 km from the smelter. As control area, a non-cadmium-polluted village (Yantuo) was selected, located 40 km from the smelter. It is similar to the polluted areas in many conditions (e.g., social, economic, and living habits) except that there is a low cadmium concentration in rice, according to a pilot study performed in preparation of this study. Based on information available in registries kept by local authorities, the population characteristics of each area were described including age, sex, and birth rate. Only persons who were born in the respective areas and had lived there and consumed locally grown rice for their entire lifetime (except the last 2 years in the highly polluted area) were included in this study. All participants were 35 years or older. Subjects with impairment of kidney or liver, hyper-parathyroidism, and those who had received drugs known to alter bone metabolism were excluded. Thus, a total of 790 participants (302 men; 488 women), were included in the present study. Subjects participating in the study completed a questionnaire to obtain information on medical and drug history, cigarette smoking, alcohol consumption, and reproductive variables in women. Data concerning fractures were obtained by questionnaire and ascertained by physician or hospital diagnosis based on X-rays.

Bone densitometry and quality control

Bone mineral density (BMD) was measured in each subject by single photon absorptiometry (SPA, SPA-4 densitometer; Chinese Measurement Technology Institute, Beijing, China) at the distal one-third of the radius and ulna. Measurement precision, expressed as the CV, was within 2%. The system was calibrated every day, the machine operator was experienced and all the bone measurements were made by the same operator. Repetition of the measurements in the same person eight times showed that the repeatability of the results was 99.66%. The change in forearm bone density was used as a marker of bone damage.

Analyses of cadmium in urine and quality control

Timed urine samples were obtained in acid-washed containers that were stored in the frozen state (-20 °C) until analysis. The urinary cadmium concentration was analyzed after digestion, using graphite furnace AAS (atomic absorption spectroscopy). Analytical quality assurance was taken into account by using standard addition on each sample and by comparison with other laboratory as described in detail by Jin *et al.* (2002). The cadmium content of urine was expressed as micrograms per gram creatinine and used as a measure of internal dose.

Statistical analysis

Database management and statistical analysis was performed using Epi-Info(Centers for Disease Control, Atlanta, GA, USA) and SPSS (SPSS Inc, Chicago, IL, USA) software. The data in BMD were normally

distributed; all results are expressed as the mean ± SD. Means and proportions were compared by using the standard normal F test and X^2 test for trends, respectively. The nominal significance level was set at 0.05. The statistical methods used also included linear regression. A stepwise procedure was used to select independent variables in multiple regression, and only those explanatory variables for which $p \leq 0.05$ were included in the regression model.

Ethical consideration

Local ethics committees of The Medical Faculty, Umeå University and Shanghai Medical University gave permission to perform the study. This study was also carried out with the permission of the local authority and conformed to local guidelines for human investigation. All participants in this study were informed about the content and the objectives of the study and gave their informed consent to participate.

Results

Summary of characteristics of participants

The total number of participants was 790, including 320 in the control area (females: 201; males:119), 208 in the moderately polluted area (females: 135; males: 73) and 262 in the highly polluted area (females: 152; males: 110). There were no significant differences in age, weight, height, body mass index (BMI), age at menopause, and years since menopause in the three different areas. The proportion of males who were current smokers at the time of the bone density measurement was higher in the heavily polluted areas than the other two areas ($p < 0.05$). There were also statistically significant differences between the moderately polluted area and the other two areas with regard to alcohol consumption in males, but no such difference was found in females. Urinary cadmium concentrations of residents in high (11.18 μg/g creatinine) and medium (3.55 μg/g creatinine) exposed areas both for males and females were significantly higher than those in the control area (1.83 μg/g creatinine), and concentrations in the high exposure group were higher than in the medium exposure group (Jin *et al.* 2002). Thus, the inhabitants of all three areas had similar baseline characteristics apart from exposure to cadmium.

BMD in participants from the three different areas

The average BMD in young adults (aged from 30 to 39 years old) in the three different areas have been measured. The value of the average and standard deviation in forearm bone mineral density (0.7980 ± 0.0710 g/cm^2 for males; 0.7117 ± 0.0663 g/cm^2 for females, Wang *et al.* 2003) was used as the baseline for the diagnosis of osteoporosis in the different areas.

The average BMD and the percentage bone loss compared with those of normal young adults of both sexes are shown in Figure 1. In women, the BMD of the forearm declined with age ($P < 0.05$) in all areas. The value of BMD in women under 60 years of age declined by up to 2–10%, and there was no statistically significant difference between the control, moderately polluted, and heavily polluted areas. In women over 60 years of age, however, the decline in BMD in the heavily polluted area was greater than those in the control and moderately polluted areas. It can also be seen that the loss of bone with age in men was lower than that in women in all areas and is the same as that in the population in the area not polluted with cadmium in men under 60 years of age. However, the decline in the value of BMD in men over 70 years of age in the heavily polluted area was greater than that in the control area ($P < 0.05$).

Stepwise regression showed that forearm bone density was decreased linearly with age ($P < 0.01$), increased with body weight ($P < 0.001$), and decreased with urinary cadmium in men ($P < 0.05$), and decreased linearly with both age ($P < 0.01$) and urinary cadmium ($P < 0.001$) in women (Wang *et al.* 2003).

Prevalence of osteoporosis and fracture in the three different areas

Based on WHO criteria, whereby BMD < -2.5 SDs below the normal young adult value is the recommended definition of osteoporosis, the prevalence of osteoporosis in subjects over 50 years old in the different areas was calculated (Wang *et al.* 2003). In males, nine cases (14.1%) of osteoporosis occurred in heavily polluted area and six cases (8.7%) occurred in the control area. The odds ratio (OR) value was 1.72 (95% CI: 0.5, 5.9) for the highly polluted area compared with the control area. In females over 50 years old, the prevalence of osteoporosis increased from 34.0% in the control area to 51.9% in the heavily polluted area, and the difference was statistically significant. The OR value was 2.09 (95% CI: 1.1, 4.0) for the

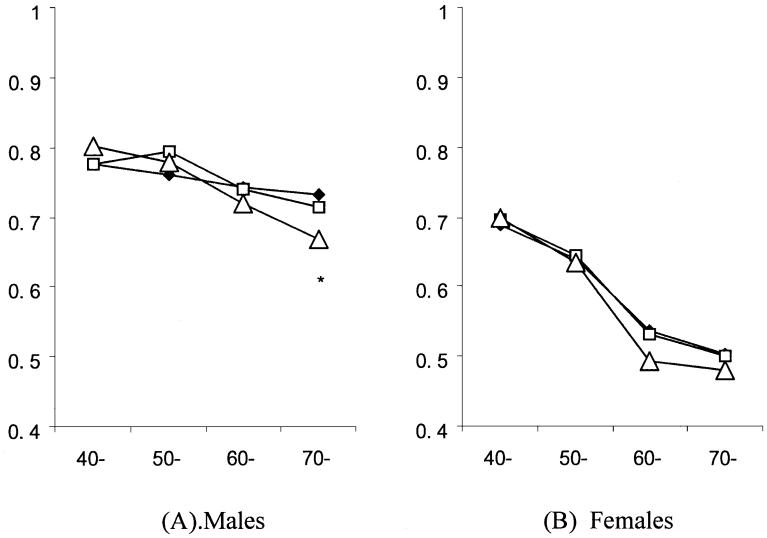

Fig. 1. Average bone density in the control (♦), moderately(□) and heavily (△)polluted areas. X axis is age group (years)and Y axis is bone mineral density (g/cm^2). *$P < 0.05$ for the difference between the heavily polluted and control areas for the same age group.

highly polluted area compared with the control area. This difference was more marked in subjects over 60 years old; the prevalence of osteoporosis increased from 8.5% in the control area to 20.5% in the heavily polluted area in males and from 55.8% to 79.5% in females.

The prevalence of spontaneous fracture in subjects over 40 years old in the different areas was estimated (Wang *et al.* 2003). Seventeen bone fractures occurred in males and 33 in females. Fractures resulting from major trauma, such as in car accidents, were excluded. As a result, the prevalence of bone fracture in males increased from 4.2% in the control area to 9.1% in the heavily polluted area, and the age standardized relative risk (SRR) value was 4.1 (95% CI: 1.55-6.61) for the highly polluted area compared with the control area, whereas in females, the prevalence increased from 4.5% to 13.8% and the SRR value was 2.5 (95% CI: 1.42-3.54) for the highly polluted area compared with the control area.

Discussion

Exposure to cadmium (Cd) causes skeletal impairments such as osteoporosis and osteomalacia (Noda & Kitagawa 1990). In 1942, cadmium-induced bone disorders were reported by Nicaud & Lafitte (1942) in French cadmium workers. Osteoporosis is a common metabolic disease, which is becoming increasingly common throughout the world as the population ages and lifestyles change. Apart from the effect of pathophysiology and genetics, many other factors may be responsible for the occurrence of osteoporosis, such as environmental factors, occupational factors, diet, etc.

The main focus of our study was the detection of cadmium-induced bone effects. The bone density of the radius and ulna, measured by SPA-4 single-photon absorptiometry, was used as a marker of skeletal damage, and cadmium in urine was used as a measure of the dose received. The results showed that, the values of forearm BMD in men over 70 years age in the heavily polluted area were significantly lower than those in the control area ($P < 0.05$). In subjects over 60 years of age of both sexes, the decline in BMD with age in the heavily polluted area was larger than that in the control area ($P < 0.05$). In both sexes, forearm BMD was correlated with age ($P < 0.001$) and urinary cadmium ($P < 0.01$ in females and $P < 0.05$ in males). This suggests that a dose-effect relationship exists between cadmium dose and BMD, and that exposure to cadmium accelerates bone loss with aging, as previously reported by Järup *et al.* (1998) and Staessen *et al.* (1999).

Based on the criteria used to diagnose osteoporosis, the results showed that, among subjects over 50 years old, the prevalence of osteoporosis in women increased from 34.0% in the control area to 51.9% in the heavily polluted area ($P < 0.01$). The same tendency existed in men, with the prevalence increasing from 8.7% in the control area to 14.2% in the heav-

ily polluted area, but was not statistically significant. Thus the prevalence of osteoporosis in the heavily polluted area is much higher than that in the control area, but women were more susceptible to the demineralising effects of cadmium on bone tissue because of the menopause (Kono *et al.* 1956). There were no significant differences in geographical and economic conditions, lifestyle, and nutrition status between the three areas. Although the proportion of males who were current smokers differed between the polluted areas and the control area, rice is the main food in all these areas and is the major source of cadmium intake. Smoking is a source of cadmium exposure, but no tobacco is produced in these areas and only commercial cigarettes are smoked. The average cadmium concentration of eight different commercial cigarettes, which are usually used by local residents, was determined and found to be 1.50 mg/kg in 1995. For a person who smoked 20 cigarettes per day for 25 years, the uptake of Cd from smoking was calculated to be about 4.05 mg, which is much lower than cadmium uptake from food. So smoking does not have much influence on the value of total cadmium uptake in the present study.

However, the results showed that the decline of BMD with age in the heavily polluted area was greater than in the other two areas and the prevalence of osteoporosis was highest in the heavily polluted area. The most striking observation in the present study was the marked increase in the prevalence of fracture in both sexes in cadmium-polluted areas, with environmental exposure to cadmium being associated with an increased risk of fractures in both women and men.

It was concluded that moderate to heavy environmental exposure to cadmium is associated with an accelerated bone loss and increased bone fragility, especially in females and in the elderly. Thus, it is important to find effective methods to preventing the bone dysfunction caused by cadmium not only in the occupationally but also in people exposed environmentally.

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References

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

Berglund M, Akesson A, Bjellerup P, Vahter M. 2000 Metal-bone interactions. *Toxicol Lett* **15**, 219–225

Chalkley SR, Richmond J, Barltrop D. 1998 Measurement of vitamin D3 metabolites in smelter workers exposed to lead and cadmium. *Occup Environ Med* **55**, 446–452

Consensus development conference 1993 Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med* **94**, 646–650

Jin T, Nordberg M, Frech W, Dumont X, Bernard A, Ye A, Kong Q, Wang Z, Li P, Lundstrom NG, Li Y, Nordberg GF. 2002 Cadmium biomonitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad). *BioMetals* **15**, 397–411

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, Alfven T, Persson B, Toss G, Elinder CG. 1998 Cadmium may be a risk factor for osteoporosis. *Occup Environ Med* **55**, 435–439.

Kjellström T. 1985 Appendix: Itai-Itai disease. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF (eds.) *Cadmium and Health: A Toxicological and Epidemiological Appraisal, Exposure, Dose, and Metabolism*. CRC Press, Boca Raton, FL, USA, 257–290

Kjellström T. 1986 Effects on the bone, on vitamin D, and calcium metabolism. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF. (eds.) *Cadmium and Health: Effects and Responses*. CRC Press, Boca Raton, FL,USA, 111–158

Kjellström T. 1992 Mechanism and epidemiology of bone effects of cadmium. In: Nordberg GF, Herber RFM, Alessio L., Eds. *Cadmium in the Human Environment: Toxicity and Carcinogenicity*. IARC Scientific Publications, vol. 118. 301–310, Lyon, France.

Kono M, Yoshida T, Sugihara H. 1956 Report on so-called Itai Itai disease-First report. *J Jpn Orthop Assoc* **30**, 100–101

Nicaud P, Lafitte A. 1942 Les troubles del intoxication chronique par le cadmium. *Arch Mal Prof* **4**, 192–202.

Noda M, Kitagawa M. 1990 Clinical investigations. A quantitative study of iliac bone histopathology on 62 cases with Itai-itai disease. *Calcif Tissue Int* **47**, 66–74

Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J, Fagard R. 1999 Environmental exposure to cadmium, forearm bone density, and risk of fractures: Prospective population study. *Lancet* **353**, 1140–1144

Wang, H., Zhu, G., Shi, Y., Weng, S., Jin, T., Kong, Q., Nordberg, G. F. 2003 Influence of environmental cadmium exposure on forearm bone density. *J. Bone Miner. Res.* **18**, 553–560