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Cadmium, osteoporosis and calcium metabolism

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Abstract

Occupational exposure to cadmium has for long been associated with renal tubular cell dysfunction, osteomalacia with osteoporosis, hypercalciuria and renal stone formation. High environmental exposure in Japan resulting from a stable diet of cadmium contaminated rice caused itai-itai disease, fractures occurring mainly in elderly multiparous women, with a form of osteomalacia, osteoporosis and renal dysfunction.

More recently a population based study in Europe, in the vicinity of zinc smelters has shown that low to moderate exposure to cadmium, with a mean urinary excretion of cadmium of the order of 1 μg/g creatinine has been associated with a decrease in bone density, an increased risk of bone fractures in women and of height loss in men. In a population-based study of residents near a cadmium smelter in China, forearm bone density was shown to decrease linearly with age and urinary cadmium in both sexes, suggesting a dose effect relationship between cadmium dose and bone mineral density. A marked increase in the prevalence of fractures was shown in the cadmium-polluted area in both sexes. Concentrations of cadmium in blood and urine were taken as exposure biomarkers, and β_2-microglobulin, retinol binding protein and albumin as biomarkers of effect. A marked dose response relationship between these indicators of exposure and effect was shown.

Hypercalciuria, which may progress to osteoporosis, has been taken as a sensitive renal-tubular biomarker of a low level of cadmium exposure. Cadmium may also act directly on bone. Animal studies have shown cadmium to stimulate the formation and activity of osteoclasts, breaking down the collagen matrix in bone.

Osteoporosis is the main cause of fracures in post-menopausal women, a common occurrence worldwide, giving rise to disability and a high cost to health services. The identification of cadmium, an environmental pollutant, as one causal factor is highly significant in helping to control the incidence of this complex condition.

Introduction

Cadmium occurs naturally in rocks and soils, usually in concentrations of less than 1 μg/g, with uptake by crops and vegetables grown for human consumption. Uptake in crops can increase following acidification by acid rain. Anthropogenic sources, as in the application of fertilisers and sewage sludge to land, industrial production of cadmium containing products, the disposal of waste waterways, smelter emissions and atmospheric deposition from cadmium plants has resulted in uptake of cadmium from food and water. In the general population the diet, and in particular the vegetable/grain component represents the major source of cadmium exposure. However, in heavy smokers cadmium uptake following inhalation exceeds uptake from all other sources. Following occupational exposure, inhalation is the principal source of cadmium exposure, which used to be heavy before adequate control measures were instituted.

Cadmium nephropathy was first described in alkaline battery workers in Sweden (Friberg 1948). Subsequent studies have shown the presence of tubular proteinuria following both occupational and environmental exposure to cadmium. The excretion of protein of low relative molecular mass, characterised by β2-microglobulin and retinol binding protein was shown to be due to the failure of the proximal tubules to reabsorb protein filtered through the Glomeruli (Bernard *et al.* 1976). With the progression of cadmium nephropathy, aminoaciduria, glucosuria, increased excretion of calcium, phosphorus and uric acid with

decreased concentrating ability of the kidney develops – signs of the acquired Fanconi Syndrome. The disturbance in calcium and phosphorus metabolism may progress further to a demineralisation of bone, and the formation of kidney stones (Friberg *et al.* 1974).

Calciuria and bone effects in cadmium workers

An increased frequency of renal stone formation in cadmium workers was first reported more than 50 years ago (Friberg 1950). Subsequently it was reported in 44% of a group of workers exposed to cadmium dust for more than 15 years gave a history of renal stone, composed mainly of basic calcium phosphate (Ahlmark *et al.* 1961). It was noted that the higher prevalence of renal stones occurred in workers without proteinuria. Friberg *et al.* (1974) commented that effects on calcium excretion in cadmium workers may occur at an early stage of exposure.

In a follow up study of 9 of 12 workers with long term exposure to cadmium fume and dust, and to cadmium sulphide dust, six men had tubular proteinuria and hypercalciuria when first seen. Sixteen years later, with persistent tubular proteinuria, hypercalciuria and additional evidence of renal tubular cell dysfunction, two had become recurrent stone formers and four had evidence of osteoporosis (Kazantzis 1979). One worker, who had experienced severe pain and weakness in the right leg had developed osteomalacia. Radiological examination showed Looser's zones in the neck of the right femur and shaft of the left fibula indicative of osteomalacia, bilateral renal calcification, nephrocalcinosis and osteoporosis. Iliac crest biopsy showed osteoid seams confirming the diagnosis. Multiple renal tubular defects involving both the proximal and distal tubule were present. In addition to tubular proteinuria, glycosuria and aminoaciduria, plasma phosphate and potassium levels were close to the lower limit of normal, with abnormally low levels on some occasions. Six cases of osteomalacia had also been reported previously in nickel cadmium battery workers with 8 to 16 years exposure, but investigation of tubular function had not been performed (Nicaud *et al.* 1942).

Itai-itai disease in Japan, osteomalacia and osteoporosis

An outbreak of multiple bone fractures, pain and disability affecting mainly middle aged and elderly women in the rural Jinzu basin in Japan in the late 1940's came to be known as itai-itai or ouch-ouch disease. The principal findings on investigation were the presence of renal tubular dysfunction, in particular β2-microglobulin in the urine, and pseudofracture characteristic of osteomalacia, together with severe skeletal decalcification, indicative of osteoporosis. The Jinzu river basin had been polluted by cadmium sludge, dumped from zinc mine, taken up in the soil by rice plants, rice being a principal source in the diet of the exposed population. Cadmium levels in rice were of the order of 0.68 mg/kg compared with 0.066 mg/kg. Initially doubt existed on the role of cadmium as a causal factor in the aetology of itai-itai disease. Alternative hypotheses were that itai-itai disease was a type of nutritional osteomalacia such as that seen in Europe during the Second World War, and that osteomalacia and rickets in children had been endemic in other areas of Toyama Prefecture where no cadmium pollution had been observed. Another hypothesis postulated that itai-itai disease was a combination of the cadmium induced and nutritional theories, as some cases did not exhibit renal dysfunction. A fourth hypothesis considered that itai-itai disease was primarily related to osteoporosis. In the itai-itai disease area both clinical and subclinical osteoporosis had existed. The osteoporotic changes due to cadmium could have advanced the appearance of osteomalacia from a subclinical to a clinical status. As renal tubular changes cause osteoporosis, the aetiology of itai-itai disease could be related primarily to the underlying osteoporosis rather than to osteomalacia (Tsuchiya 1978).

In osteoporosis the mass of bone is reduced, causing increasing bone fragility, but its composition is normal. This reduction results from an imbalance between the formation and resorption of bone, which occurs with increasing age, more rapidly in women than men. At a population level, osteoporosis tends to be diagnosed following a fracture resulting from a fall, or where backache is associated with vertebral collapse, the development of kyphosis and loss of height.

Investigating the possible role of cadmium in the aetiology of osteoporosis, as in all epidemiological studies, account has to be taken of possible confounding factors. In addition to age related bone loss, accelerated bone loss may follow immobilisation, as in rheumatoid arthritis. Rapidly progressive osteoporosis may follow severe injury in the young, associated with enforced immobilisation. In such cases hypercalcaemia or hypercalciuria may also occur. Bone

loss has also been observed in space travellers. Certain endocrine disorders may also cause osteoporosis. Undiagnosed thyrotoxicosis has given rise to hypercalcaemia, hyperphosphatemia and hypercalciuria. Hypopituitarism and hypogonadism have been associated with osteoporosis, and iatrogenic osteoporosis has followed the prolonged administration of corticosteroids. Cigarette smoking, while being an important source of cadmium intake, is also independently associated with bone loss and thus is a significant confounder of the relationship between cadmium exposure and bone loss. Dietary factors, in particular calcium intake and genetic differences are also relevant.

The presence and extent of osteoporosis may be estimated objectively by measurement of bone mineral density (BMD). Different methods are available. Dual X-ray Absorptiometry (DXA) and Single Photon Absorptiometry (SPA) have been used to estimate bone mineral density. The stiffness (STIFF) as an index of bone mass has been estimated on calcaneal bone using an ultrasound method (Honda *et al.* 2003). STIFF inversely correlated with cadmium in urine suggesting a significant effect of cadmium on bone loss in women without signs of cadmium-induced kidney damage.

Cadmium exposure and bone effects in Belgium

A population based study was carried out to investigate whether environmental exposure to cadmium may lower bone density and increase the risk of fractures (Staessen *et al.* 1999). The study was carried out on residents in ten districts in a rural area in Begium, six of which bordered on three zinc smelters. (The Phee-Cad project). The study population were randomly selected participants in an earlier, cross-sectional Cadmium in Belgium (Cadmibel) study. In the Cadmibel study, after adjustment for confounders, urinary calcium rose by 0.25 mmol daily for each two-fold increment in urinary cadmium excretion (Staessen *et al.* 1991). Residents in the polluted areas had urinary cadmium, and evidence of renal tubular dysfunction with raised urinary excretion of β2-microglobulin, retinol binding protein and N-acetyl-β-glucosamidase (Staessen *et al.* 1994).

In the Phee-Cad study Cadmibel participants collected a 24-hour urine sample for cadmium excretion. Bone density was measured at the forearm above the wrist by single photon absorptiometry (SPA). Body height was measured on each participant, and data on the incidence of fracture by questionnaire. Information was collected on participants' lifestyle in terms of physical activity, smoking and alcohol intake and on participants' menopausal status. Soil samples and leek and celery samples were analysed for cadmium from gardens owned by participants. Altogether, 506 of the 1014 Cadmibel participants provided the required data, whose exposure to cadmium was environmental alone. The principal findings in this study showed that in postmenopausal women a two-fold increase in cadmium exposure was associated with a decrease in proximal and distal bone density by nearly 0.01 g/cm^2.

Excluding major trauma such as car accidents, 20 bone fractures had occurred in men and 24 in women. Height loss exceeded the 90% percentile occurred in 20 men and 31 women. In stepwise Cox regression a two-fold increase in cadmium excretion correlated with 73% increased risk of fracture in women and with a 60% increased risk of height loss in men. In addition, urinary cadmium was replaced as the biomarker of internal exposure by each person's external exposure, defined as the geometric mean concentration of cadmium in the soil and in vegetables, leek and celery, sampled in the relevant district of residence. For both men and women external exposure to cadmium was a significant predictor of the incidence of fractures and of height loss. Urinary cadmium excretion in the residents of the six districts near the smelters was 22.8% higher than in the inhabitants of the four other districts. Residence in a more polluted district increased the risk of fractures. Overall, this study showed that low to moderate environmental exposure to cadmium as shown by urinary excretion is associated with an increased risk of fracture in women and possibly with a raised risk of height loss in men. Men and women in this study had a mean urinary cadmium excretion of only about 1 μg/g creatinine, compared with a mean urinary cadmium excretion of nearly 30 μg/g creatinine in Japanese patients with itai itai disease.

Osteoporosis in Chinese population groups exposed to Cadmium

A large scale epidemiological study has been carried out on residents of two cadmium contaminated areas in South East China and of a nearby control area (Nordberg *et al.* 2002). River water used for irrigating rice fields had been polluted by effluents from a Zn and Pb smelter which functioned since 1961. The study population included those aged 36 years or older

who had lived in the area since birth, all of whom had consumed locally grown rice. Forearm bone density was measured by single photon absorptiometry (SPA) at the distal third of radius and ulna, renal dysfunction by determining urinary concentration of retinol binding protein and cadmium in blood and urine by atomic absorption spectrometry.

Statistically significant dose effect and dose response relationships were found between cadmium in blood and cadmium in urine and an increased excretion of retinol binding protein as an indicator of renal dysfunction. As bone mineral density decreases after the menopause, postmenopusal women were considered separately. Postmenopausal women showed a significantly lower bone mineral density with urinary cadmium above 20 μg/g creatinine or with blood cadmium above 20 μg/g. Men with a blood cadmium above 20 μg/g also exhibited significantly lower bone mineral density. Similar findings followed a dose response analysis with in addition, an increased prevalence of low bone mineral density in premenopausal women.

A further large-scale epidemiological study was performed in this area in South East China, in control, moderately and heavily cadmium polluted areas, bordering on a non-ferrous smelter. The study population was as reported above (Nordberg *et al.* 2002). A quality control programme was conducted to determine analytical quality in the determination of cadmium in blood and urine and for β2-microglobulin, creatinine and albumin in addition to retinol binding protein as indicators of effect (Jin *et al.* 2002). Analytical quality rarely reported in previous studies on cadmium was shown to be adequate. In the highly exposed area most of the cadmium in blood values were higher than 5 μg/l and most of the cadmium in urine values were higher than 5 μg/g creatinine. The indicators of effect: β2-microglobulin, retinol binding protein and albumin in urine, were all significantly higher in the heavily polluted area than in the control area.

Forearm bone density was measured by single photon absorptiometry at the radius and ulna and participants completed a questionnaire (Wang *et al.* 2003). The decline in bone mineral density with age in the heavily polluted area was significantly greater than that in the control area for subjects over 60 years of age of both sexes. Bone density decreased linearly with age and urinary cadmium in both sexes suggesting a dose-effect relationship between cadmium dose and bone mineral density. The prevalence of osteoporosis in women increased from 34% in the control area to 51,9% in the heavily polluted area in subjects over 50 years old. Furthermore there was a marked increase in the prevalence of fractures in both sexes in the cadmium-polluted area.

Osteoporosis in a Swedish population group exposed to cadmium

Relatively low level exposure to cadmium, early kidney damage and osteoporosis have been identified in an extensive cross-sectional study of more than 1000 people living in Southern Sweden in the vicinity of a nickel cadmium battery plant. Both environmentally and occupationally exposed persons were included in the study to obtain a wide range of cadmium exposures (Alfvén *et al.* 2000). Urinary cadmium, α-microglobulin as an indicator of renal tubular damage and bone mineral density using dual energy x-ray absorptiometry were estimated. In the age group 60 years and over with urinary cadmium over 3 nmol/mmol creatinine there was a threefold increased risk of low bone mineral density and an increased risk of forearm fractures compared with the lowest dose group. The study showed lower levels of cadmium than previously anticipated to be a risk factor for the development of osteoporosis (Järup 2002).

Mechanisms explaining effects of cadmium on bone

Calcium metabolism ensures calcium homeostasis in health. Plasma calcium is maintained within a narrow range 2,10–2,60 mmol/l, by balance between calcium absorption in the intestine, calcium excretion in the urine and calcification and decalcification of bone. The major fluxes of calcium are regulated by parathyroid hormone (PTH), which increases renal tubular reabsorption of calcium and bone resorption; calcitonin, which inhibits bone resorption and vitamin D which augments intestinal absorption of calcium. PTH acts on proximal and distal tubules of the kidney to increase renal tubular reabsorption of calcium and to depress the tubular reabsorption of phosphate. This leads to a rise in plasma calcium and a fall in plasma phosphate.

A major stimulus to the secretion of calcitonin is an increase in serum calcium concentration. Calcitonin inhibits osteoclast activity and this lowers serum calcium, thus having an action opposite to that of PTH

Table 1. Potential mechanisms for cadmium effects on bone. (Kjellstrom 1986)

1.	Interference with PTH stimulation of vitamin D activation in kidney cells.
2.	Reduced activity of kidney enzymes hydroxylating 25-HCC to 1,25-DHCC.
3.	Increased urinary calcium excretion.
4.	Reduced absorption of calcium from intestines.
5.	Interference with calcium incorporation into bone cells.
6.	Interference with collagen production in bone cells.

with respect to maintenance of plasma calcium. Vitamin D derived from the diet and from the skin by ultraviolet irradiation of 7-dehydrocholesterol undergoes a series of metabolic conversions by hydroxylation mainly in the kidney to the active form calcitriol (1,23 dihydroxy vitamin D3). The principal effects of calcitriol on calcium metabolism are to increase intestinal absorption of calcium and phosphate and to increase reabsorption of bone mineral matrix.

A series of animal experiments together with observations on cadmium exposed people with renal tubular damage and control groups suggest six possible mechanisms for cadmium effects on bone (Kjellstrom 1986) – Table 1. The complicated interactions between cadmium exposure and calcium and vitamin D metabolism can explain the findings of osteomalacia and osteoporosis (Kjellstom 1992). Observations indicate that a cadmium induced reduction in the hydroxylation of 25-HCC to the active form 1,25 DHCC occurs following renal tubular damage by cadmium. The decreased activation of vitamin D due to cadmium induced renal tubular damage has been considered to be crucial for the induction of the bone effects of cadmium.

Hypercalciuria, which may progress to osteoporosis has been taken as a sensitive renal tubular biomarker of low level cadmium exposure in the general population. However, osteoporosis may also result from impaired calcium uptake, for cadmium reduces the generation of active vitamin D in the renal tubular cells.

Cadmium may also act directly on bone. An *in vitro* study of culture of a clonal osteogenic cell showed that the mineralisation of the cells was significantly decreased following the addition of cadmium ions, together with a decrease in collagen content and alkaline phosphatase activity. The study indicates that cadmium may interfere directly with the mineralisation of bone cells (Miyahara *et al.* 1988).

A transient increase in calcium excretion has been shown to follow a single oral cadmium dose in mice. Animal studies have shown cadmium to stimulate the formation activity of osteoclasts, breaking down the collagen matrix in bone to release calcium into blood. Cadmium has also been shown to activate two types of gene expression pathways in bone cells early after exposure, protective pathways that counteract the toxic effects of cadmium including metallothionein induction and toxic response pathways involved in stimulation of osteoclast bone resorption (Bhattacharyya *et al.* 1988).

Osteoporosis is the main cause of fractures in postmenopausal women, a common occurrence world wide, giving rise to disability and a high cost to health services. While endocrine, genetic and lifestyle factors may be the main risk factors for osteoporosis, the identification of cadmium, an environmental pollutant, as one causal factor, would be highly significant in helping to control the incidence of this complex condition.

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