Cadmium-induced osteomalacia

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ABSTRACT The detailed study of a battery plate maker, who had worked with cadmium for 36 years, showed that proteinuria, typical of renal tubular dysfunction, had been observed for 25 years and during the last 12 years of his life the patient had suffered increasing disability from gross bone disease. Several bone biopsies and detailed metabolic studies showed typical severe osteomalacia, which responded well initially to calcium and vitamin D treatment. Examination of the liver both in life and after death showed a gross excess of cadmium. This was also found in the kidneys after death. Previously unreported changes were present in the bones, especially the lumbar vertebrae which were probably more the result of gross bone deformity than cadmium deposition. The mechanism of development of the severe acquired Fanconi syndrome was thought to be a combination of dietary calcium and vitamin D deficiency and impaired calcium absorption from abnormal vitamin D synthesis, related to the cadmium deposition in the renal tubules, which also caused the defect in renal tubular reabsorption.

Persistent proteinuria in workers exposed to cadmium dust was first described by Friberg¹ and later observed in those engaged in various industrial processes using cadmium.²⁻⁵ The urine protein is predominantly of low molecular weight characteristic of proximal renal tubular dysfunction.^{6,7}

The major clinical effects of exposure to cadmium have usually been described as respiratory disturbances, and the proteinuria has been regarded as benign. Secondary effects of the nephropathy, such as renal calculi, have been reported.⁸ Adams *et al*⁵ described preliminary studies on a cadmium worker with severe osteomalacia who had spent 30 years in the industry, and Kazantzis⁴ reported similar findings in a single worker. The extreme rarity of the condition as an industrial hazard and increasing interest in the possible association of cadmium intoxication and bone disease in Japan (itai-itai disease⁹) and elsewhere justified a fuller account of the patient previously reported by Adams *et al*.⁵

Case history

The man, born in 1905, started work as a battery plate maker in 1929 and worked continuously in the industry until his retirement in 1965, much of the

time on night shift. His first complaint in 1963 was of continuous pain in the legs and hips of gradually increasing severity. In 1965 he suffered a spontaneous fracture of the femur after a minor fall. This was treated in hospital with pinning and traction, but healing was slow, and the pin was removed. He remained bed-ridden until August 1967 when further fractures occurred, and he was admitted to this hospital.

He was then completely disabled, with gross flexion deformities of both hips and severe wasting of the quadriceps. He was obese, with a blood pressure of 130/85 mm but with no other physical abnormalities. The proteinuria was less than 1.0 g/24 h, with a typical renal tubular pattern of small molecular weight protein. There was slight impairment of renal function with a raised alkaline phosphatase (table 1). Radiological examination showed fractures of the right femoral neck and upper shaft and in the left femoral subtrochanteric area. There were multiple rib fractures. Both right and left tibial shafts showed fractures, and the proximal ulnar shafts at the site of insertion of the biceps muscles into the radius were similarly affected. The skull was normal. The spine showed loss of definition of both compact and endosteal bone in the vertebrae but no vertebral collapse. There were no changes of hyperparathyroidism and no Looser's nodes.

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Table 1 *Clinical chemistry findings*

Date	Serum chemistry							Urine				
	Urea (mmol/l)	Creatinine (μ mol/l)	Calcium (mmol/l)	Phosphate (mmol/l)	Alkaline phosphatase (KA units)	Albumin (g/l)	pH	Standard bicarbonate (mmol/l)	Total protein (g/24 h)	Calcium (mmol/24 h)	Phosphate (mmol/24 h)	Lysozyme (μ g/ml)
23 Aug 1967	12.1	234	2.3	0.9	49	45	7.35	19.0	1.0 T	2.1*	17.0*	—
6 Oct 1967	12.1	220	2.4	0.9	40	45	7.31	18.0	1.2 T	3.6*	16.1*	140
9 Feb 1968	9.5	176	2.5	1.2	47	39	—	—	1.1 T	9.0*	15.9*	67
1 Nov 1968	9.8	184	2.6	0.9	15	42	7.4	22	0.9 T	—	—	56
2 Jan 1969	11.3	237	2.5	1.2	21	43	—	—	1.2 T	—	—	—
10 Dec 1969	9.5	240	2.5	1.0	26	49	7.35	20	—	—	—	—
10 Mar 1970	9.0	220	2.3	0.7	13	45	—	—	—	3.5*	21.7*	85
22 Oct 1971	9.0	228	2.3	0.8	15	41	—	—	1.2 T	—	—	65
20 Feb 1974	10.1	202	2.3	0.8	48	43	7.35	20	1.1 T	—	—	46
4 Jan 1975	10.1	220	2.4	1.0	39	40	7.4	21	0.7 T	—	—	—
11 Aug 1976	11.1	210	2.1	1.0	24	28	7.35	19	1.2 T	—	—	75
25 Aug 1976	13.6	202	2.1	0.9	25	27	—	—	1.0 T	—	—	—

T = Tubular, small molecular weight, proteinuria present.

* = Balance data—five days means.

Bone biopsy indicated moderately severe osteomalacia with cancellous bone trabeculae covered by uncalcified osteoid tissue 36–54 μ m thick. There was no evidence of osteoporosis or lacunar reabsorption.

The dietary history indicated a remarkably low calcium and vitamin D intake. He had worked at night for many years and did not eat butter or margarine, preferring lard or dripping, and he had an unusually low milk intake. In all other respects, however, his nutrition appeared unremarkable.

Calcium balance studies (table 2) showed a low calcium excretion in the urine and radioisotope ^{47}Ca

uptake was decreased. The patient was treated with calcium lactate 6 g and vitamin D 50 000 units daily. There was some improvement in his condition with reduced bone pain during the following five months. He was readmitted for further calcium balance studies and assessment in February 1968.

At that time renal function was unchanged, and there was no reduction of the alkaline phosphatase (table 1). The bone deformities were unaltered, but osteogenesis was pronounced at the fracture sites. The spine films showed increased density of both compact and endosteal bone. The calcium supplement was

Table 2 *Calcium, phosphorus, and nitrogen balance*

		Intake	Output		Total	Balance
			Urine	Faeces		
22-25 Sep 1967	Calcium (mg)	2070	63	1144	1207	+863
	Phosphorus (mg)	2540	723	673	1396	+1144
	Nitrogen (g)	20.95	14.50	1.05	15.50	+5.44
26-29 Sep 1967	Calcium (mg)	2070	64	1114	1208	+862
	Phosphorus (mg)	2540	728	673	1401	+1139
	Nitrogen (g)	20.95	14.53	1.05	15.53	+5.42
23-26 Feb 1968	Calcium (mg)	3590*	200	2750	2950	+640
	Phosphorus (mg)	1688	343	1185	1528	+160
	Nitrogen (g)	14.34	9.53	12.15	10.74	+3.5
27 Feb-1 Mar 1968	Calcium (mg)	3590*	513	2705	3218	+372
	Phosphorus (mg)	1688	685	1104	1789	-101
	Nitrogen (g)	14.34	12.30	11.70	13.47	+0.87
6-9 Nov 1968	Calcium (mg)	3940*	473	999	1472	+2468
	Phosphorus (mg)	2847	637	470	1107	+740
	Nitrogen (g)	14.23	12.54	0.77	13.31	+0.92
10-13 Nov 1968	Calcium (mg)	3940*	480	1400	1880	+2060
	Phosphorus (mg)	2847	717	620	1337	+1510
	Nitrogen (g)	14.23	11.14	1.07	12.21	+2.01
14-17 Nov 1968	Calcium (mg)	3940*	536	1423	1959	+1981
	Phosphorus (mg)	2847	558	441	999	+1848
	Nitrogen (g)	14.23	12.20	8.3	13.03	+1.2
18-21 Nov 1968	Calcium (mg)	3940*	466	1266	1732	+2208
	Phosphorus (mg)	2847	550	386	936	+1911
	Nitrogen (g)	14.23	9.62	7.5	10.37	+3.86

*Includes calcium lactate 6 g/day supplement.

Fig 1 Undecalcified section of second iliac crest biopsy (1976) stained by von Kossa's method to show osteoid seams. ($\times 250$.)

continued as calcium gluconate 2 g/day but the calciferol was stopped in November 1968 after 12 months' treatment because of the danger of vascular calcification. The bone radiographs then showed further evidence of healing, and the alkaline phosphatase had returned to normal concentrations (table 1).

The patient remained disabled and unable to walk largely because of the gross bone deformities. Bilateral hip osteotomies and a left tibial osteotomy were performed in 1970 from which he made a satisfactory recovery apart from a postoperative pulmonary embolus. Bone biopsy at this time showed some osteoporosis with no osteoid seams. The renal function showed no changes from 1968 to 1976, and the tubular proteinuria remained unchanged. He remained in reasonable health, although severely disabled, until in 1975 he developed a mild left-sided hemiplegia and again became immobile. In July 1976 he suffered a further fracture of the left tibia and fibula, and the bone density was again much reduced. Old healed fractures were present in many bones, together with more recent non-united fractures of the left tibia and fibula. Bone biopsy again showed osteomalacia, although less severe than in 1967 (fig 1). The osteoid seams were less extensive, measuring up to $35\ \mu\text{m}$ in width in places. There was osteoblast activity but no osteoclasts.

His condition deteriorated, and he died in August 1976 after a cardiac arrest. There had been no significant change in renal function or in the proteinuria since his first admission in 1965. The blood pressure had gradually risen to levels around 160/100 mm in the two years before his death, but had not required treatment.

Postmortem findings

The vascular system showed extensive atheromatous changes, particularly severe in the basilar artery and middle cerebral arteries of the brain, the left coronary, and in all the great vessels. There were multiple atheromatous aneurisms in both thoracic and abdominal aorta, which were filled with laminated blood clot.

The kidneys were small, weighing 55 g and 80 g with a finely granular appearance, but no other macroscopic abnormality. The heart was much enlarged with left ventricular hypertrophy and dilatation and with ischaemic fibrosis of the left ventricular wall. The bones were very soft with thin, widely spaced trabeculae. No specific changes were present in other organs.

Histological findings

The lung showed dilatation of the alveolar ducts consistent with age changes. A few muscular pulmonary arteries showed cellular intimal thickening resulting from old organised pulmonary emboli. The kidneys showed severe postmortem autolysis. There was recognisable chronic ischaemic damage, with numerous small scattered groups of completely hyalinised glomeruli in the subcapsular zone with interstitial lymphocytic infiltration about these areas. The remaining glomeruli were normal. The autolytic changes made assessment of the renal tubules impossible. The small arteries showed pronounced fibroelastic intimal thickening due to age changes. The undecalcified sections of bone showed mild osteomalacia, with thin osteoid seams, much less pronounced than in the bone biopsies.

The bone of the vertebral bodies showed an irregular pattern of trabeculae in the cancellous bone, the trabeculae being thicker than normal and irregularly curved (fig 2). One striking finding in the vertebral bodies was the unusual appearance in numerous areas of thin, short irregular fragments of lamellar bone, which appeared as if splintered off the normal trabeculae. The bone marrow in these fairly sharply demarcated areas showed fat globules greatly reduced in size from normal marrow together with cells containing a finely foamy cytoplasm resembling small areas of fat necrosis. There were also in these areas apparently single fibres of striated voluntary muscle (fig 3). The significance of these most unusual areas is uncertain. They were distributed towards the upper and lower surfaces of the vertebral bodies and thus resembled the microfractures described by Vernon-Roberts and Pirie,¹⁰ but unlike these lesions there was no evidence of healing.

Fig 2 Decalcified sections of vertebral bodies showing wide trabeculae with a rather irregular pattern. (Haematoxylin and eosin $\times 100$.)

The other unusual features were the extensive new formation of sub-periosteal woven bone, much of it uncalcified—that is, severe osteomalacia (fig 4). There were also occasional small solid nodules consisting of packed lamellar bone with wide osteoid seams on the surface (figs 4 & 5).

Calcium balance and calcium uptake studies

Calcium balances were performed in the metabolic ward after three-day equilibration periods on measured diets shortly after admission, and after six months' and twelve months' treatment with calcium and vitamin D (table 2). The major features of these

Fig 3 An area in a vertebral body showing pronounced abnormal variation in size of fat globules in marrow and thin short fragments of lamellar bone. Sharply curved U-shaped structure in centre is a voluntary muscle fibre. ($\times 620$.)

Fig 4 An area of normal compact cortical bone (on left of photograph) showing a thick irregular layer of woven bone on surface which is due to pronounced osteomalacia. ($\times 250$.)

balance studies were the strong positive balance of calcium throughout and the initial remarkably low urine calcium excretion in the two balance periods in September 1967. Excessive urinary loss of calcium was never present, even on high calcium intakes. The rate of calcium retention was significantly greater during the periods on vitamin D and calcium treatment even after 12 months' treatment when radiological bone healing was also present.

Radioactive ^{47}Ca was given by mouth as calcium chloride in September 1967 ($5 \mu\text{C}$ dose) when the plasma activity/litre after 60 minutes was only 1.19% of the dose and after three hours was 1.56%. The whole body retention of the dose was 37.4% at seven

Fig 5 An abnormal solid nodule of bone in cancellous bone. It is attached to a trabeculus of normal cancellous bone (right) and consists of lamellar bone arranged in small circumferential patterns. ($\times 250$.)

days. These results all indicated severe impairment of calcium absorption rather than excessive urinary loss. The calcium uptake measurement was not repeated after vitamin D treatment as the positive calcium balances suggested adequate absorption on an increased calcium and vitamin D intake. The observed improvement in bone density on x-ray and the diminution in the width of the osteoid seams on the bone sections, also indicated satisfactory absorption and repair of the bone structure.

Renal function tests

The serum creatinine and urea concentrations remained slightly raised, and the creatinine clearance lowered to a mean of 30 ml/min throughout the nine years of observation. There was a small protein loss in the urine, never exceeding 1.5 g/day, which had been present at least from 1952, when regular tests were started by the factory medical officer. The urine protein, at least from 1955, showed the characteristic pattern of small molecular weight protein loss associated with proximal tubular abnormality. The clearances of lysozyme, ribonuclease, and two other small molecular weight proteins were always grossly raised to levels seen only in renal tubular abnormalities.^{5,7} The predominance of small molecular weight proteinuria was confirmed by G200 Sephadex gel filtration on several occasions. Excess amino-aciduria was shown by two-dimensional paper chromatography, and glucose was intermittently present in the urine. These findings are characteristic of the adult Fanconi syndrome and were present unchanged from 1956 until the patient's death in 1976, without any significant deterioration of renal function.

Cadmium studies

Exposure to cadmium had been prolonged and exceptionally heavy in this patient because of his many years' employment in the factory, particularly during the years 1939-45 and on subsequent permanent night shift.

Table 3 *Cadmium content of whole body and organs at necropsy*

Tissue	Atomic absorption $\mu\text{g Cd/g wet wt}$ (= ppm)		Neutron activation (ppm)
	Patient	Control (normal)	
Kidney	77	12	80 $\pm$ 20
Liver	172	<3	210 $\pm$ 6
Spine	8.3	0	26 $\pm$ 13
Rib	3.2	0	Not examined
Femur	2.1	0	Not examined

Liver cadmium concentration was measured in life in June 1974 by the non-invasive technique of neutron activation analysis.¹¹ This "activates" the ¹¹³Cd isotope present in the liver to produce a "prompt" energy-specific gamma quantum, which may be identified and measured.¹² The patient was unable to lie on the measuring couch in the optimum position for accurate measurement because of his considerable physical disabilities, but a very prominent cadmium peak was recognised over the liver and estimated to be at least 100 parts per million, the normal limit being under 5 ppm.

Urinary excretion of cadmium was measured in 1972 and 1975 and was only 36 $\mu\text{g/l}$ and 21 $\mu\text{g/l}$ respectively. These relatively low values were obtained some years after exposure to cadmium had ceased and are probably not of great significance.

Tissue cadmium studies were also performed in 1976 on tissue examined at necropsy. The same technique of neutron activation analysis was used with idealised geometry. Chemical analysis of cadmium was carried out on the same samples (King 1976, personal communication) and are compared in table 3.

The ratio of kidney cadmium:liver cadmium is usually 10:1.¹³ The results show a reversal of this ratio to 1:2.5, a finding that has been noted in Japanese studies.¹⁴ Liver cadmium concentrations were extremely high at 200 ppm, although renal cadmium content was much lower, and the total kidney cadmium of 10.8 mg is within the range for "normal" non-industrially exposed men.¹⁵

Discussion

Renal tubular dysfunction of the type shown by this patient is a well-recognised result of chronic cadmium exposure in man and animals. The continuous loss in the urine of small quantities of protein having the characteristic pattern of small molecular weight components (tubular proteinuria) may persist in cadmium workers for many years after exposure has ceased, and has usually been regarded as a relatively benign abnormality. Detailed studies of renal tubular function have shown increased loss of phosphate, glucose, and amino-acids^{4,5} characteristic of proximal convoluted tubular dysfunction.

The fully developed adult Fanconi syndrome with osteomalacia in addition to the urinary abnormality appears to be extremely rare in industrial cadmium workers. Six patients with varying severity of bone disease including Looser's zones and osteoid seams were described in France by Nicaud *et al.*,¹⁶ but no studies were made of the proteinuria. A brief preliminary account of the subject of this detailed report was given by Adams *et al.*,⁵ and a further single case

was reported by Kazantzis.¹⁷ Several careful surveys of factory workers exposed to cadmium have failed to show further patients with clinical or radiological bone disease.¹⁸ In the cadmium workers studied by Adams *et al*⁵ only one other patient had mild osteomalacia, which was thought to have resulted from the effects of a partial gastrectomy rather than from cadmium.

The evidence for prolonged cadmium absorption in the subject of this report is conclusive. The gross elevation of cadmium in the liver at necropsy by both neutron activation and chemical atomic absorption is characteristic of prolonged exposure. The somewhat lower amounts in the kidney are explained by the excretion of relatively large amounts of cadmium in the urine, especially in those patients with proteinuria.² The actual urinary cadmium excretion was recorded in 1972 at 38 $\mu\text{g/l}$ and in 1975 at 21 $\mu\text{g/l}$ and while both these levels were considerably above normal excretion in individuals who have not been exposed to cadmium, they were not excessively high. A relation between urinary cadmium excretion and kidney cadmium content has been observed in industrial workers who do not show proteinuria, but this ceases after the onset of proteinuria, which occurs when a critical tissue cadmium concentration has been reached.¹⁹ Thus neither the absolute tissue concentration of cadmium nor the urinary excretion in a given individual provide evidence of the actual duration or severity of exposure, nor are these measurements related to the severity of the clinical signs.

It is justifiable to inquire, therefore, whether some special factor was present in the patient described to account for his severe bone lesions. The duration of exposure was not appreciably longer than others in the same factory without bone lesions.⁵ Dietary histories are notoriously inaccurate, but there was an indication of unusually low calcium and vitamin D intakes, and the prolonged work on night shifts could possibly have aggravated the vitamin D deficiency still further. The calcium balance studies showed remarkably low calcium excretion together with an impaired calcium uptake from the intestine, similar to the findings in other patients with the Fanconi syndrome.²⁰ The response to vitamin D in modest dosage with an increased calcium intake was also similar to that seen in other renal tubular defects and did not suggest a primary malabsorption defect, since substantial clinical, radiological, and bone biopsy improvement occurred after treatment in 1967. Unfortunately the very gross deformities caused by the bone condition necessitated numerous operations, and the eventual relapse of the osteomalacia was almost certainly due to immobility and a low dietary intake of calcium and vitamin D.

The development of severe bone disease in patients with proved cadmium nephropathy is therefore probably due to several different factors, as has been suggested in the similar occurrence of osteomalacia mostly in middle-aged multiparous women in several well-defined geographical areas of Japan (itai-itai disease). A significant increase in renal tubular abnormalities has been observed in these areas together with a high cadmium content of local rice, vegetables, and drinking water.⁹ The incidence of renal tubular dysfunction increased with age and with duration of exposure but was not invariably associated with osteomalacia. Kitamura²¹ and others have claimed that the cadmium concentrations in food and water are irrelevant and that the osteomalacia resulted solely from vitamin D and other dietary deficiencies, although they give no explanation as to why the osteomalacia is much less frequent in other parts of the country where similar dietary and nutritional factors prevail.

The precise relation of the presence of cadmium in the renal cortex and renal tubular defects of reabsorption remain unexplained. Proximal tubular reabsorption of glucose, amino-acids, phosphate, and small protein molecules appears to be an active process mediated by intracellular enzyme transport specific to certain chemical groupings. Many conditions causing damage to proximal tubular cells have been shown to interfere with this process of reabsorption—for instance, acute tubular necrosis, paraproteinaemia, degraded tetracycline, and heavy metal poisoning, especially with bismuth, copper, and lead. In most of these conditions, however, the tubular defect appears to be reversible when the underlying cause is removed. The remarkable duration of the effect of cadmium on tubular reabsorption without demonstrable damage to glomerular function or the development of progressive interstitial fibrosis produced by other toxic substances, such as analgesic drugs, remains completely unexplained.

The demonstration of the synthesis of active 1:25 dihydrocholecalciferol by the renal tubules²² and the possible inhibition of this process in renal tubular defects²³ raises the possibility that cadmium may also act as a cellular enzyme inhibitor as well as its proved effect on tubular reabsorption of small molecular weight proteins, amino-acids, glucose, etc. The problem of the extreme rarity of the bone abnormalities in industrial exposure, where tubular abnormalities are relatively common, still remains unexplained. A combination of prolonged loss of phosphate from tubular dysfunction, reduced active vitamin D synthesis in the renal tubules, and dietary factors seems the most likely, if somewhat unsatisfactory explanation of the severe and totally

disabling disability resulting from prolonged cadmium exposure in the occasional patient.

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