# *Toxic effect of aluminium and other substances on bone turnover*

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**RESUMEN**

**Efectos tóxicos del aluminio y otras sustancias sobre el metabolismo óseo.**
*El aluminio es capaz de inhibir la normal mineralización ósea y provocar osteomalacia, la que además, si bien con una frecuencia menor, puede ser también inducida por otros elementos como el hierro y el flúor.*

**SUMMARY**

**Toxiv effects of aluminium and other substances on bone turnover.**
*Aluminium may lead to the development of osteomalacia since it inhibits bone mineralisation by blocking calcium uptake into bone. Moreover, osteomalacia may also develop, though much less frequently, due to the toxic effects on mineralisation of other elements such as iron and fluoride.*

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## Normal bone turnover

In the normal adult skeleton bone is continually being remodelled so that at any one time many small parts of trabecular and cortical bone are being removed by osteoclasts while at other previously — resorbed sites matrix is being replaced by osteoblasts. As it has been outlined in this issue by Dr. Boyle, these two processes appear to be coupled to one another with resorption preceding formation. Replacement of bone matriz, however, appears to occur more slowly than its removal and thus in normal bone unmineralised matrix (osteoid) may cover up to 25 % of the trabecular surface while less than 8 % is undergoing resorption.

In end-stage renal failure, secondary hyperparathyroidism leads to a pronounced increase in bone remodelling so that the number and size of sites undergoing resorption and formation increase. Thus, in a typical case of osteitis fibrosa osteoid may cover around 60 % of the trabecular surface while 10-20 % may be undergoing resorption. If Vitamin D or calcium deficiency accompany this increased bone turnover, newly formed osteoid may fail to mineralise resulting in the development of osteomalacia.

## Aluminium bone disease

During the late 1960's it emerged that some dialysis patients developed a form of osteomalacia that did not respond to treatment with Vitamin D and was associated with bone pain and fracture. Some of these patients also suffered from the dialysis encephalopathy syndrome [1] and had been dialysed with water containing high levels of aluminium. The osteomalacia was eventually attributed to aluminium toxicity following the detection of high levels of aluminium in serum and bone biopsy specimens by means of neutron activation analysis (NAA) [2] and electrothermal atomic absorption spectrophotometry (ETAAS) and the demonstration of aluminium along the calcification front at the interface between thickened osteoid seams and calcified bone matrix by means of electron probe x-ray micro-analyse [3, 4]. The localisation of aluminium along the calcification front was later demonstrated by histochemical staining which has now replaced NAA, ETAAS and electron micro-probe analysis as the best and most convenient method for detecting aluminium toxicity.

## Bone Histology

Aluminium toxicity can lead to two main types of histological abnormality in bone. In one, thick osteoid seams are present, often focally distributed along trabecular surfaces (Fig. 1). This is in contrast to Vitamin D — related osteomalacia in which the thickened seams cover most of the bone surface. In the second type osteoid seams are of normal thickness and typically cover much of the bone surface (Fig. 2). In both forms there is little evidence of active bone resorption and aluminium is detectable along the calcification front and also along cement lines within calcified bone. We have recently reviewed bone biopsy specimens from 75 cases of histologically-proven Al toxicity that occurred in Glasgow between 1981 and 1984 and found that 41 % had thickened osteoid while osteoid was of normal thickness in the remaining 59 %. The explanation for the different appearances remains unclear but they may perhaps be due to differences in the degree of secondary hyperparathyroidism prevailing at the onset of aluminium toxicity. In a further 21 biopsy specimens aluminium was present along cement lines but not at the calcification front. In most of these cases there was mild or moderate osteitis fibrosa suggesting that Al toxicity had existed previously and that increased bone turnover had since been re-established.

The presence of aluminium along cement lines within fully calcified bone matrix indicates that mineralisation of osteoid can occur despite the inhibitory effect of aluminium at the calcification front. A striking feature in some biopsy specimens is a rather unusual form of mineralisation within thickened osteoid seams. It takes two main forms. In one, small foci of calcification are seen around osteoid osteocytes (Fig. 3) and in the other large bands of pale-staining calcification extend down to the underlying cement line (Fig. 4). Thus, aluminium lines may become entrapped in fully calcified bone as a result of calcification beginning around the osteoid osteocytes with thickened osteoid seams and extending widely within the osteoid down to the aluminium line.

## Biochemical findings

In established cases of Al-related osteomalacia bone turnover is decreased so that typically there is minimal active production of matrix by "plump" osteoblasts and minimal osteoclastic bone resorption. Both of these features reflect the suppression of parathyroid hormone (PTH) secretion either directly by Al or else indirectly by the effect of hypercalcaemia [5] which is a frequent complication. The development of hypercalcaemia is promoted by a number of factors including the presence of aluminium at the calcification front, where it blocks the uptake of calcium into bone, by the addition of calcium to the dialysis fluid and by treatment with active Vitamin D metabolites. In most cases, aluminium toxicity can be identified as the cause of the hypercalcaemia since, in contrast to autonomous (or tertiary) hyperparathyroidism, PTH and alkaline

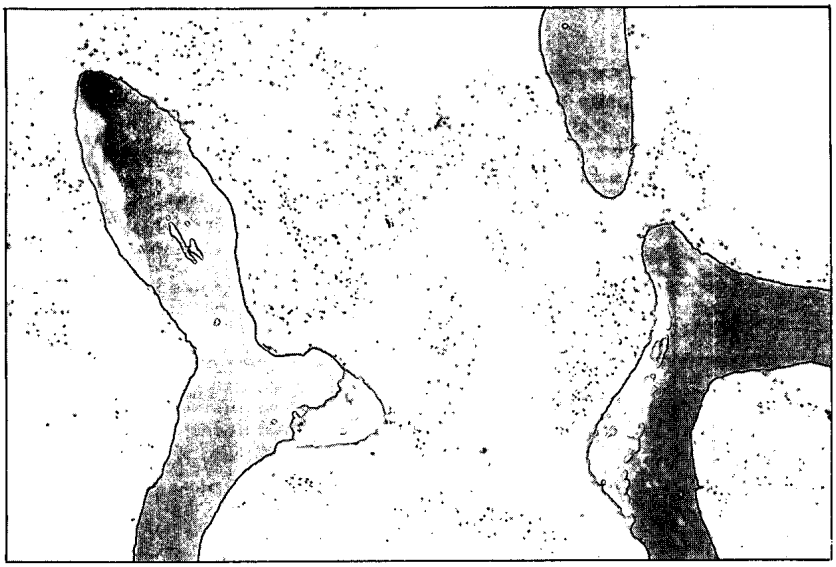

*Fig. 1.—Undecalcified section of iliac bone from patient with Al-related osteomalacia. Pale-staining, thickened osteoid seams are focally distributed along trabecular surface with normal bone resorption (1 % toluidine blue).*

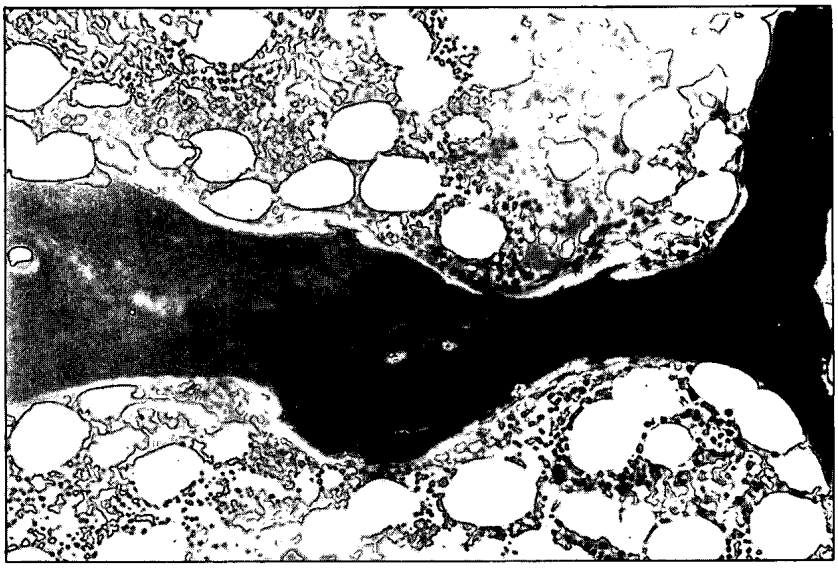

*Fig. 2.—Undecalcified section of iliac bone from patient with Aluminium toxicity. Pale-staining, thin osteoid seams cover most of the trabecular surface with normal bone resorption (1 % toluidine blue).*

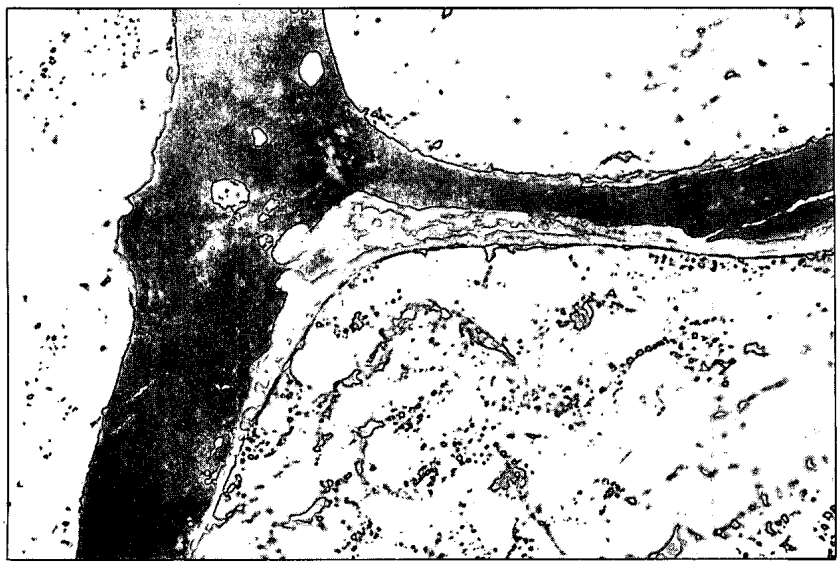

*Fig. 3.—Undecalcified section of iliac bone from patient with Al-related osteomalacia. Patchy, light-staining calcification is present within thickened osteoid seams (1 % toluidine blue).*

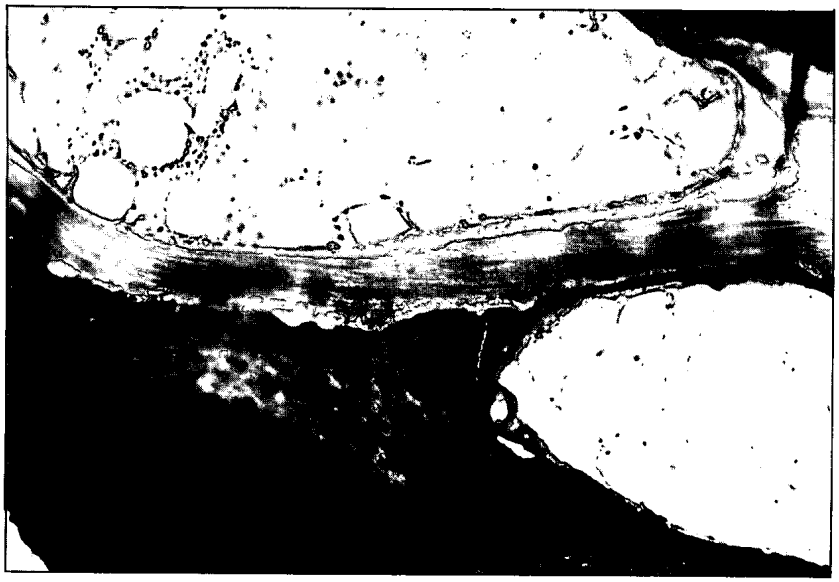

*Fig. 4.—Undecalcified section of iliac bone from patient with Al-related osteomalacia. Light-staining calcification is more uniformly distributed within thickened osteoid seam and extends down to Aluminium line (not seen) at the cement line (1 % toluidine blue).*

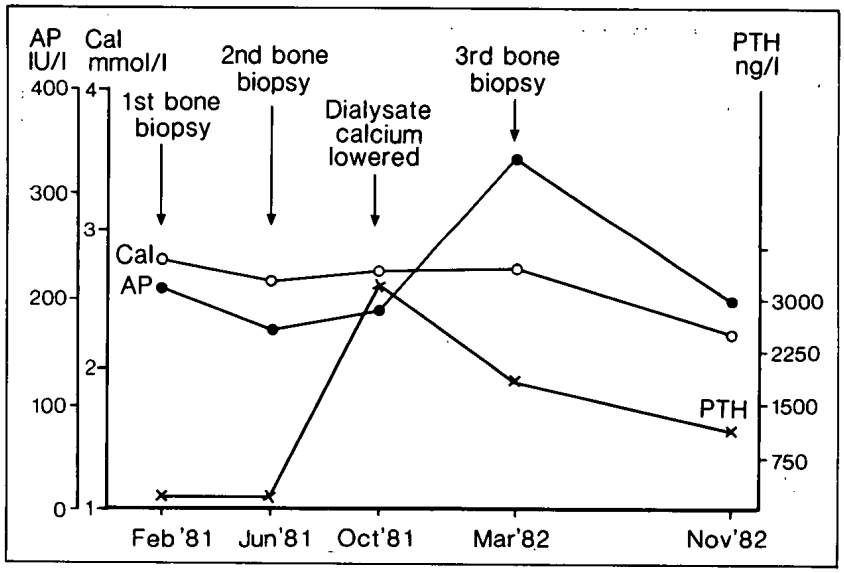


*Fig. 5.—Biochemical findings in a patient with hypercalcaemic Al-related osteomalacia. Histological and biochemical findings at 1st and 2nd bone biopsies were typical for Al-related osteomalacia. Stopping oral $Al(OH)_3$ and lowering dialysate calcium resulted in histoligical improvement with return of secondary hyperparathyroidism and eventual lowering of serum calcium to normal range.*
*Normal ranges: Alkaline phosphatase (AP), 30-120 units/l; calcium (Cal), 2.2-2.6 mmol/l; parathyroid hormone (PTH) undetectable, 600 ng/l.*

phosphatase (AP) levels in serum are low. However, in a number of cases PTH and alkaline phosphatase levels may be elevated and bone biopsy is required to differentiate between Al toxicity and tertiary hyperparathyroidism.

The distinction is not always straight forward since the timing of the biopsy in relation to the onset of aluminium toxicity and to changes in aluminium exposure is crucial. The problem is illustrated in figure 5. This patient had been receiving regular haemodialysis for three years before her first bone biopsy in February 1981. Hypercalcaemia (2.78 mmol/l) was accompanied by normal PTH and only slightly elevated serum AP levels. Bone biopsy showed extensive aluminium staining, thickened osteoid and normal bone resorption. The serum aluminium level was 3.7 µmol/l. Thus, the biochemical and histological pictures were typical of Al-related osteomalacia. Al levels in the dialysis water were low (generally less than 1 µmol/l) and oral aluminium — containing phosphate binders were stopped. At bone biopsy four months later the histological and biochemical picture showed little change apart from a fall in the serum Al level. Two months later, however, the PTH level had risen to 3,200 ng/l and the biochemical picture now suggested tertiary hyperparathyroidism. Had bone biopsy proof of Al-osteomalacia not been available this patient might have had sub-total parathyroidectomy. Instead the calcium dialysate level was lowered from 1.50 to 1.34 mmol/l. Bone biopsy taken five months later showed improvement of the mineralisation defect,

decreased aluminium staining and increased bone resorption and formation. The serum calcium level later returned to the normal range.

This case illustrates that unnecessary parathyroidectomy may be prevented in some patients if Al toxicity can be shown to be the cause of hypercalcaemia. However, the problem may be more complex. Recent reports have suggested that parathyroidectomy might actually precipitate aluminium toxicity [6, 7] and thus further study of the indications for and the effects of parathyroidectomy is required.

## Mechanism of toxic action

Although many studies have confirmed the suppressive effects of aluminium on bone mineralisation and turnover its precise mechanism of toxic action on bone remains unclear. Its accumulation at the calcification front leaves it ideally situated to interfere with mineralisation. Possible toxic mechanisms include direct physical poisoning of hydroxyapatite crystal growth [8] and inhibition of enzymes involved in mineralisation such as alkaline phosphatase [9]. The concentration of aluminium in serum or bone at which inhibition of mineralisation occurs is not known. However, our previous electron micro-probe studies [3] of bone from patients with aluminium-related osteomalacia suggests that the level may be around 4-10 mg/g dry weight in the mineralisation nuclei of the calcification front. This concentration is much higher than the levels detected by other analytical techniques such as ETAAS and NAA (typically up to 0.3 mg/g) since these measure the elemental concentration in the whole bone specimen rather than only in the sites of maximum accumulation.

## The effects of other trace elements

Although aluminium appears to be the major cause of osteomalacia and suppression of bone turnover in renal dialysis patients other elements may interfere with bone metabolism. Recent studies have shown that iron may accumulate at the calcification front [10], particularly in patients with high serum ferritin levels following multiple blood transfusions. It has been suggested that in biopsy specimens from patients with osteomalacia in which staining for aluminium is either negative or weak iron may be the cause of the mineralisation defect. However, other studies have shown that in cases where heavy aluminium staining has been seen along the calcification front adjacent sections also stained positively for iron. The relative contributions of aluminium and iron in such cases to the development of the mineralisation defect have yet to be fully elucidated. The problem is complicated by the fact that aluminium toxicity may cause an iron-unresponsive microcytic anaemia that is often treated with multiple blood transfusion. We have been unable to demonstrate iron by means of histochemical staining or electron micro-probe in any of our cases of aluminium bone disease despite the presence in some cases of high serum ferritin levels and abundant iron in marrow macrophages.

Fluoride has also been implicated in the development of dialysis osteomalacia [11]. Endemic and industrial fluorosis are characterised by osteosclerosis and osteomalacia and since fluoride is added to some public water supplies it was suggested as a possible cause of dialysis osteomalacia. Indeed a relationship was found between fluoride accumulation and the severity of bone disease in Newcastle in 1972 where the only two identifiable solutes present in excess in the public water supply were fluoride and aluminium. Since then, however, aluminium bone disease has been reported from dialysis centres such as Glasgow where fluoride is not added to the water. The observations that aluminium bone disease can develop in patients who have never been dialysed and that removal of aluminium from dialysis water prevents osteomalacia have centred the blame firmly on aluminium and taken attention away from fluoride as a possible cause. Although deficiency of or excessive exposure to other elements such as copper and beryllium could lead to osteomalacia as yet there has been no proven link between them and renal bone disease.

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