Chapter

151

Metabolic Bone Disease
(Past, Present and Future Challenges in the Management)

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INTRODUCTION

The past 40 years have seen some important historical events leading to substantial clinical and technical advances in our understanding of pathogenesis of Metabolic Bone Disease. Metabolic bone disease occurs due to alteration in calcium, phosphorous, vitamin D and parathyroid hormone metabolism and affects the skeletal system. Nutritional vitamin D deficiency osteomalacia and renal bone disease are the most common metabolic bone disease that are encountered in the Indian context. The pathogenetic mechanisms have been thoroughly studied and treatment strategies devised.

Renal bone disease presents many clinical problems because of multiple pathogenetic factors, non-specific clinical symptoms as well as not precisely enough methods available for evaluating progress and treatment efficacy. Interest in renal bone disease has grown rapidly in the last few decades due to the high incidence in patients with chronic kidney disease and in those treated with repetitive dialysis and renal transplantation.

The spectrum of bone disease in CKD has changed over the years due to better management. There is at least, a consensus on the types of renal bone disease which includes mild, mixed, predominant hyperparathyroid, osteomalacia and aluminium related uremic bone disease. Recently, adynamic bone disease not related to aluminium has been reported by us in this country.

Despite extensive research on derangements of calcium and phosphate metabolism in renal failure, several unresolved issues are still with us : poor control of hyperphosphatemia, relative inefficacy of active vitamin D to prevent progressive parathyroid hyperplasia and persistence of bone disease despite lowering of PTH and vitamin D therapy.

Nutritional vitamin D deficiency osteomalacia is treated by vitamin D3 (cholecalciferol) in doses of 5,000 to 25,000 units per day along with 1-2 gm of elemental calcium supplements. Balance studies with varying doses of vitamin D suggested that Indian women needed a higher dose of vitamin D (50,000 units daily)[1] to replete the severely depleted vitamin D stores and suppression of secondary hyperparathyroidism. Eighty-six per cent patients demonstrated resistance to vitamin D action at unknown site in the absence of renal or gastro-intestinal abnormality. Prevention of nutritional vitamin D deficiency osteomalacia is recommended to exposure to ultraviolet sun-rays at least 2-4 hours per day alongwith supplementation of vitamin D in the diet, in areas where dietary intake of vitamin D is low.

Many studies demonstrated that daily calcitriol and alpha-calcidol doses below 0.25 micrograms may be valuable in the treatment of patients with mild to moderate CKD who may be at a risk of developing secondary hyperparathyroidism. It can also be prevented by early dietary phosphate restriction, use of phosphate binders and correction of metabolic acidosis.

New vitamin D analogues – OCT and peri-calcitol may be useful in the treatment of secondary hyperparathyroidism. Calcimimetics have now proved to be useful for suppressing or even replacing the potentially active vitamin D.

NUTRITIONAL OSTEOMALACIA

Inadequate vitamin D synthesis in the skin due to poor exposure to sunlight is responsible for development of nutritional osteomalacia. Low dietary intake of

vitamin D also contributes to its manifestation. Various factors such as poor socio-economic status, repeated pregnancies and lactation may be the aggravating factors[2,3].

From 1962-1980, **2703** cases proved to be that of osteomalacia. **1750** cases from these turned out to be suffering from nutritional osteomalacia (64.74%).

Majority of the cases (94.6%) belonged to age group between 13-40 years. Rest of the cases were above 41 years of age (5-6%). Most commonly seen in females (98.3%) and rarely in males (1.7%). 1358 cases (77.6%) were married and 392 cases (22.4%) were unmarried. Out of married, 70% had multiple pregnancies (>2). 30% were without pregnancies.

Majority of people lived in slums of the old Delhi area and were deprived of sun light. 57% belonged to the very poor and the rest to middle socio-economic status. 95.7% (1675 cases) came from urban area, especially those of slums of old Delhi and the walled city of Chandni Chowk. The rest were from rural areas (4.3%).

Average daily caloric intake of these patients were nearly half of that consumed by the normal group (2300 cal/day). Vitamin D intake in their diet was below 30 units/day as compared to normal group (more than 95 units/day).

Clinical features: Backache, specially in the lumbosacral region, was deep seated, dull and constant and also occurred in the pelvis and thigh bones. Muscular weakness, difficulty in getting up from floor and waddling gait and tetany (Fig. 1) were the most characteristic features of osteomalacia (Table 1).

Biochemical data: Majority of patients had low serum calcium, low phosphorous and low 25-OH D with raised serum alkaline phosphatase. Plasma 25-OH D was less than 3 ng/ml and 24 hr urinary calcium excretion was found to be below 50 mg/24 hours and on low calcium diet of 200 mg. There was further reduction in excretion of calcium as compared to normal.

Radiology: The pathognomonic feature of osteomalacia is the presence of looser's zone (45%) (Fig. 2). Decreased bone density was seen in all, deformed and irregular pelvis in 30% (Fig. 3) and fracture neck of femur in 6% of cases. Subperiosteal resorption in phalanges suggestive of hyperparathyroidism (Fig. 4) was seen in 50% cases. Osteitis fibrosa cystica in 1% cases.

Histology: Both decalcified and undecalcified bone sections were studied which showed evidence of osteomalacia (calcification front < 60%, wide osteoid seam > 15 um and increased osteoid volume > 2%) (Fig. 5).

Fig. 1: Picture of patients with tetany

Table 1: Presenting symptoms (Nutritional osteomalacia)

Symptoms	*%*
Aches and pains	100
Waddling gait	60
Tetany	12
Spinal deformity	10
Joint involvement	10
Knock knee	2
Cataract	2

Treatment: Vitamin D in doses of 10,000 to 50,000 units/day is given orally. Vitamin D3 now been replaced by use of vitamin D metabolites such as 25-OH D3 50 mg daily or 1,25-(OH) 2D3 (calcitriol) or it analogue (1 α D3) 0.25 to 0.5 mg daily for 4-8 weeks and monitored

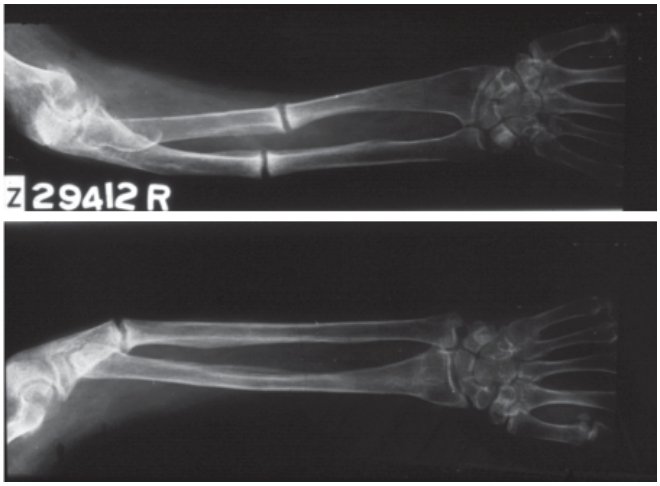

Fig. 2: Looser's zone in patients with osteomalacia

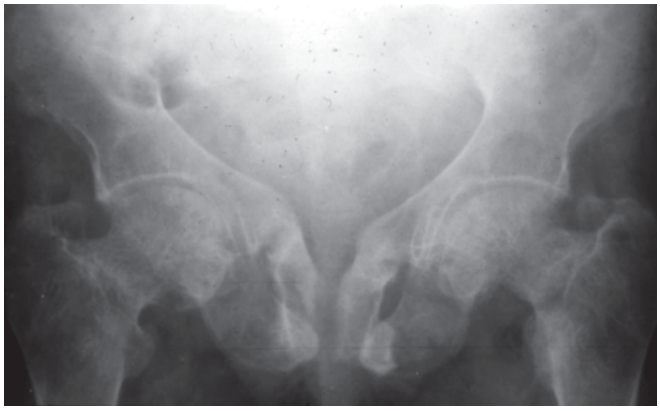

Fig. 3: Deformed or irregular pelvis

by estimation of serum calcium and plasma (25-OH D) levels. A minimum of 1-2 gm of elemental calcium is recommended per day to achieve positive calcium balance to replete the depleted stores.

Patients showed improvement in muscular weakness within 2-4 weeks of starting treatment and radiological healing of the looser's zone was also observed. Osteomalacia should be regarded as cured when bone lesions have healed and biochemical abnormalities return to normal.

RENAL BONE DISEASE

It is ubiquitous to all patients of uremia. It is probably one of the most fascinating and challenging of all metabolic bone disease and most rewarding as regard to its management.

Pathogenesis: Relatively early in advancing renal insufficiency, two central abnormalities of mineral

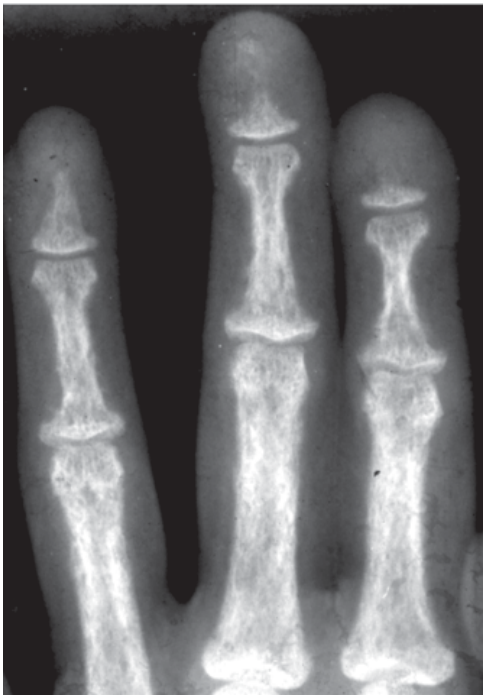

Fig. 4: Subperiosteal resorption

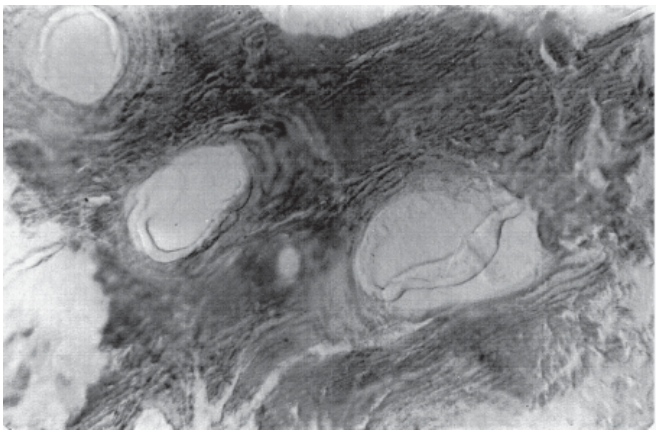

Fig. 5: Wide osteoid seam suggestive of osteomalacia

metabolism develop that contribute to the development of secondary hyperparathyroidism, i.e. hyperphosphatemia and decreased levels of 1,25 dihydroxy cholecalciferol. Secondary hyperparathyroidism causes loss of skeletal integrity and progressive development of hyperparathyroid bone disease. Besides, osteomalacia and hyperparathyroidism, metabolic acidosis and dialysis related factors including aluminium deposition contribute to various forms of metabolic bone lesions seen in chronic kidney disease (Fig. 6). 2337 cases of renal bone disease out of 3272 cases of CKD (71.42%) were studied during 1964-2006 (Table 2).

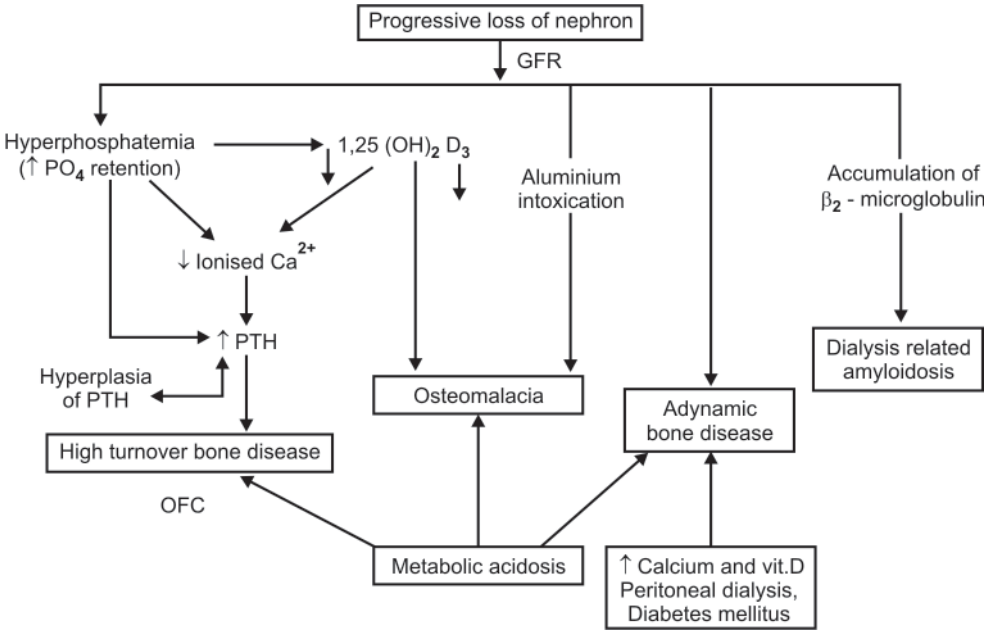

Fig. 6: Pathogenesis of renal bone disease

Table 2: Prevalence of renal bone disease

	No. of CKD	*Renal bone disease*
1964-1972	80	44 (55%)
1973-1980	160	64 (40%)
1981-1986	307	213 (69.4%)
1987-1991	300	180 (60%)
1992-1996	625	436 (66.9%)
1997-2005	800	600 (75%)
2006-	1100	800 (72.72%)
	3272	2337 (71.42%)

Table 3: Types of bone disease (CKD)

Types	*%*
Mild	9.8
Mixed	53.6
Predominant hyperparathyroid (high turnover)	7.3
Osteomalacia	26.8
Aluminium related osteodystrophy	5.5
Adynamic bone disease	2.4

Types of Renal Bone Disease

Based on histological techniques, bone diseases were classified into mild, mixed, predominant hyperparathyroid (high bone turnover osteodystrophy), osteomalacia, aluminium related osteodystrophy (low turnover osteodystrophy) and adynamic bone disease (Table 3).

Bone disease is usually asymptomatic. Symptoms appear late in the course of the disease and are nonspecific and usually subtle and insidious (60%). Patients with predominant parathyroid disease (Fig. 7) may have diffuse bone pain, myalgia and arthralgia (90%). Patients with low turnover disease (Fig. 8) have axial bone pains, muscular weakness and pathological fractures (10%). Patients with aluminium intoxication (Fig. 9) may also have neurological symptoms like dysarthria, mutism, myoclonus, seizures, dementia and hematological derangement (15%). Patients with mixed renal bone

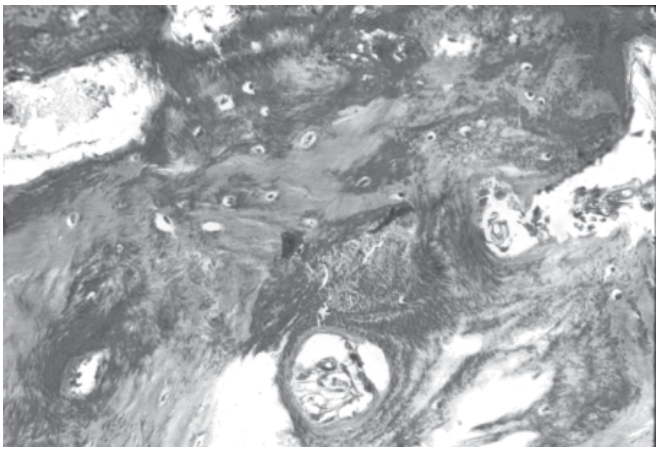

Fig. 7: Hyperparathyroid bone disease

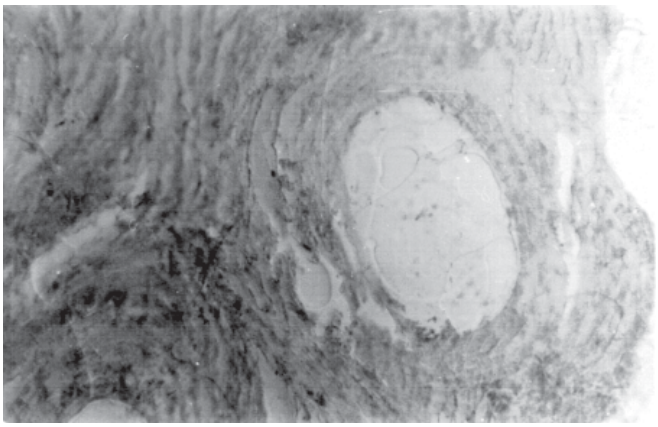

Fig. 8: Low turnover disease

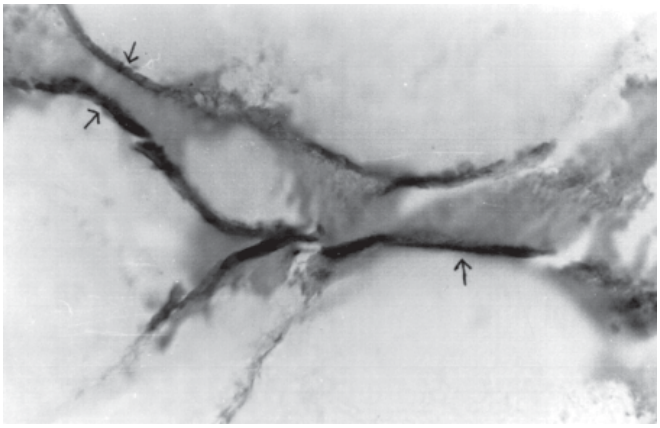

Fig. 9: Aluminium-related bone disease

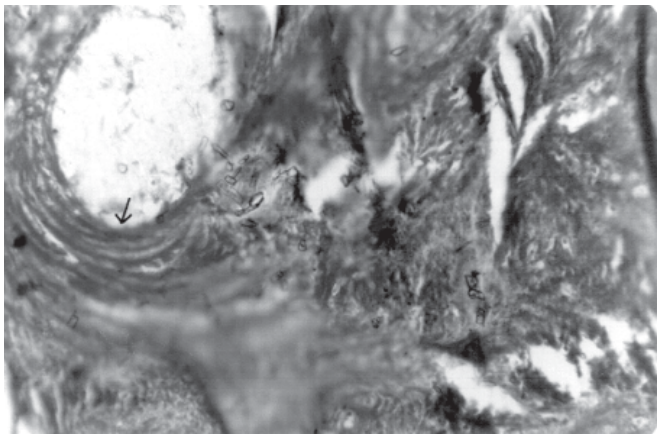

Fig. 10: Mixed uremic bone disease

disease (Fig. 10) have features belonging to both groups and those with mild disease (Fig. 11) have fewer symptoms if any.

A number of biochemical alterations (serum Ca^{2+}, PO^{43-}, serum PTH level) appear earlier in the course of

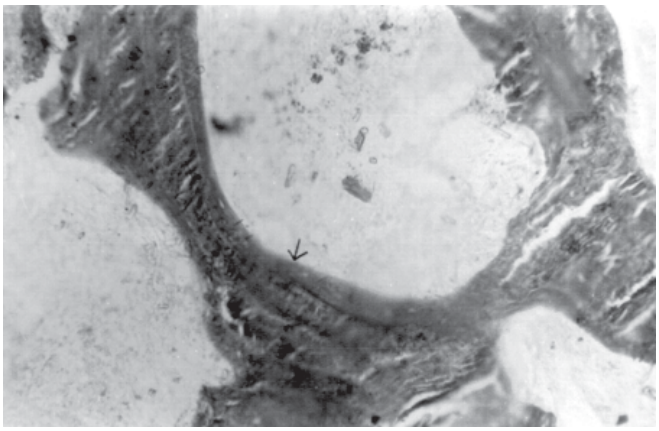

Fig. 11: Mild bone disease

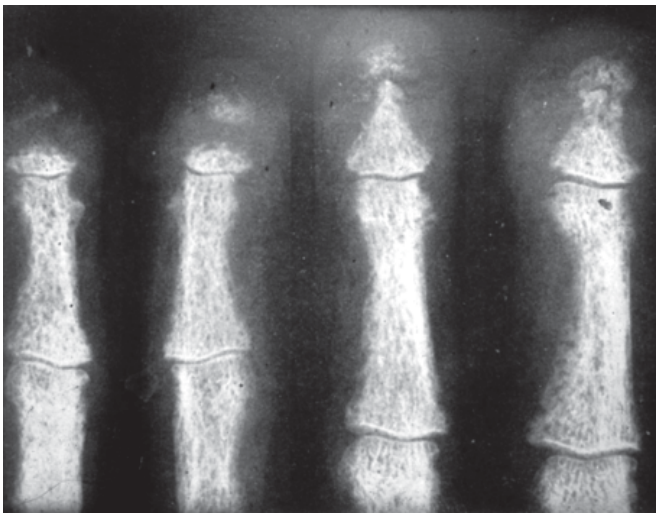

Fig. 12: Subperiosteal resorption suggestive of hyperparathyroid bone disease

progressive renal failure and reveal presence of bone disease. Osteocalcin (BGP) is a new marker of bone formation process and helpful in hyperparathyroid bone disease. Bone alkaline phosphatase is the most sensitive and specific marker for predicting the type of bone disease. Serum PICP (Procollagen Type I Carboxy-terminal) and urinary ICTP (Type I collagen-linked telopeptide) are of potential use for screening bone turnover. High serum PICP is indicative of renal bone disease and serum alkaline phosphatase is a good marker in osteomalacia.

Radiological features: The characteristic radiological feature of HPTH bone disease is subperiosteal erosion of bone (Fig. 12). Looser's zone are uncommon in renal failure and their absence not helpful in excluding osteomalacia. Rugger jersey spine is seen in 5% cases (Fig. 13).

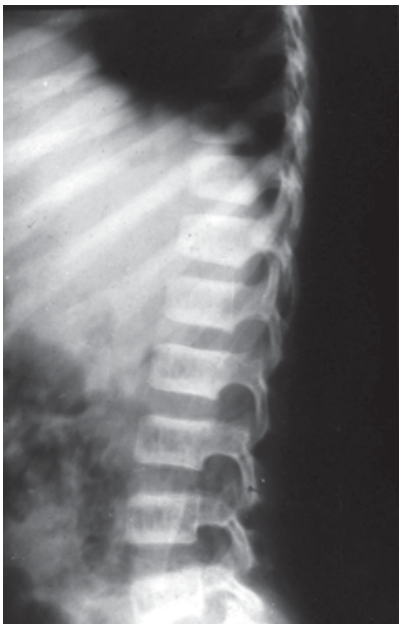

Fig. 13: Rugger jersey spine

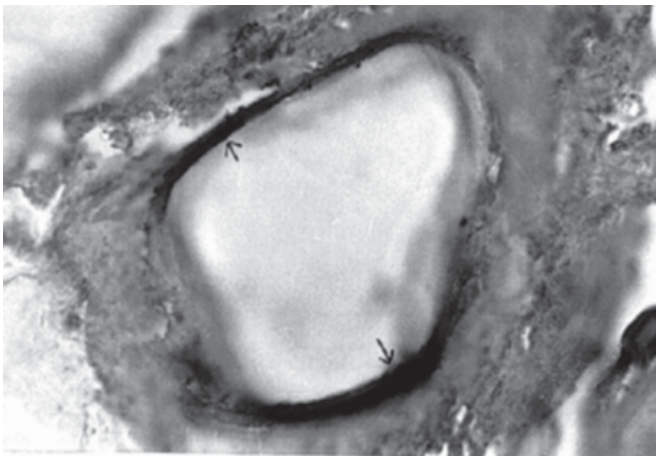

Fig. 14: Aluminium related osteomalacia

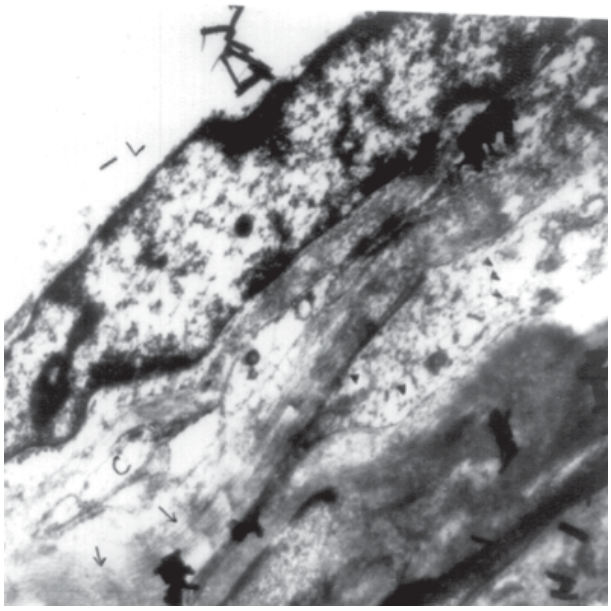

Fig. 15: Low turnover bone disease

Table 4: Serum aluminium levels and types of bone disease

Bone histology	*Serum aluminium (ng/ml)*	*Range (ng/ml)*
Normal	8.12 ± 5.41	0–18.5
Hyperparathyroid	95.67 ± 47.37	63–150
Mild	114.75 ± 29.27	79–150
Mixed	181.99 ± 64.77	97–377
Adynamic	240 ± 0	240
Osteomalacica	323.09 ± 231.97	76–760

Serum Aluminium Levels

Serum AL levels are almost always raised in renal failure. Skeletal toxicity is more closely related to its deposition at or near the surface of the mineralization front (Fig. 14). Serum AL levels correlates with bone AL content. Serum AL levels are usually elevated in subgroup of osteomalacia and adynamic bone disease and are low in secondary hyperparathyroidism (Table 4).

Electron Microscopic Changes

Electron microscopy has an edge over light microscopy in being able to reveal cellular and subcellular details of the affected tissue. Transmission electron microscopy (TEM) was studied in 30 patients with renal bone disease. This is the first kind of study done in India to highlight mechanisms of matrix deposition, calcification and resorption in patients with renal bone disease.

TEM revealed abundance of lining cells, quiescent osteoblasts and spottingly mineralized matrix in patients with low bone turnover disease (Fig. 15). In high turnover disease (Fig. 16), abundant osteoblasts and osteoclasts are found to be the hallmark of TEM picture. TEM is an effective tool in the study of structure function relationship of bone cells and matrix at a sub-cellular level[4].

Management

The specific treatment used and the intensity of the treatment will vary with the stage of renal failure, the presence or absence of the overt bone disease.

The main aim of the therapy is to keep the phosphorous levels between 4.5-5.5 mg/dl. Restrict

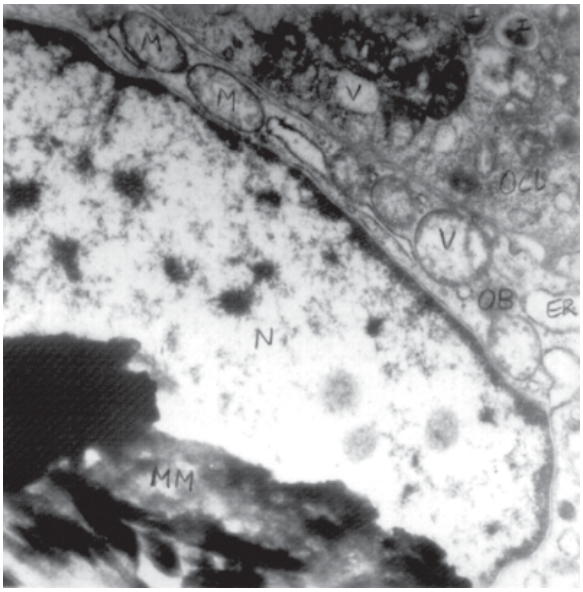

Fig. 16: High turnover bone disease

dietary phosphate intake to 600-800 mg/day, limit meat and dairy products. Prevent phosphate absorption from GIT with phosphate binders containing aluminium hydroxide, calcium carbonate, acetate are the most widely prescribed. Several new phosphate binders are now available which include Sevelamer hydrochloride and lanthanum carbonate. As patients are being dialysed, an increase in dietary phosphate to 800-1200 mg/day may be allowed. Hemodialysis removes approximately 1 gm per treatment and CAPD removes 300 mg phosphorous per day.

Control of Calcium

Current studies reveal that in mild secondary hyperparathyroidism small daily dose of oral calcitriol and alfacalcidol provide optimal benefit if given early in the course of renal insufficiency. Several highly active naturally occurring forms of vitamin D like calcifediol (25-OH D3), calcitriol (1,25(OH)2D3) and pericalcitol have been found useful in the treatment of renal bone disease. Of all these compounds, the calcitriol and 1-α-OHD3 has been most prescribed[5]. 1-2 μg of calcitriol IV. is recommended after each dialysis or oral calcitriol 2-4 μg twice a week can be prescribed. If PTH level do not fall into an acceptable range after 1 year of treatment then surgical parathyroidectomy or parathyroid gland ablation by ethanol should be considered. Calcitriol should not be used when there is hyperphosphatemia or Ca x P product more than 75. Pericalcitol and doxercalciferol analogue of calcitriol were approved in the treatment of secondary hyperparathyroidism[5].

Chelating agents (DFO) have been tried in aluminium related bone disease patients on dialysis. Repeated infusions of 30-40 mg/kg/week during the last hour of the dialysis session have been found useful. The optimal duration of DFO therapy has not firmly established and probably depends on the severity of intoxication and tissue load.

CONCLUSION

Renal bone disease continues to be a challenging clinical problem. Control of hyperphosphatemia is essential. Several unresolved issues are still with us : poor control of hyperphosphatemia, relative inefficacy of active vitamin D to prevent progressive parathyroid hyperplasia and persistence of bone disease, despite lowering of PTH and administration of vitamin D. Many new modalities are on the horizon though none appear to be well studied at this time.

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