

Review Article

Overview of Renal Osteodystrophy and Current Therapeutic Approach

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Introduction:

ROD includes all the disorders of bone and mineral metabolism, caused by impaired renal function. It represents a spectrum of bony disorders ranging from high turnover lesions of secondary hyperparathyroidism to low turnover lesions of adynamic bone and osteomalacia. In children with end stage renal failure, the most common skeletal pathology is that of secondary hyperparathyroidism.¹ Adynamic bone lesions that are not associated with aluminium deposition in bone are more common in adults with advanced renal failure. This disorder is less common in children and most such cases are due to treatment with large doses of calcitriol to control secondary hyperparathyroidism (SHPT). That means, in children ROD is mainly a consequence of impaired metabolism of Ca^{++} , PO_4 and Vitamin D and their complex interaction with parathyroid hormone, eventually causing secondary hyperparathyroidism. As the new studies suggest, the complex interaction causing the development of ROD can be summarized as follows.

- 1) There is already some degree of phosphate retention even at GFR of 50-70ml/per minute/1.73m². More phosphate retention develops as the GFR keeps falling. Retention of phosphate inhibits one- α hydroxylase enzyme needed for the synthesis of calcitriol. It also causes increased PTH secretion by a direct stimulation of the parathyroid gland (through phosphorus sensors?).
- 2) Decreased calcitriol in blood, thus decreases calcium absorption from the intestine and increases PTH secretion through vitamin D receptors in the gland.
- 3) Also decreased ionized calcium increases PTH secretion through calcium sensors in the gland.
- 4) Even with high serum PTH level, there is a skeletal resistance to its calcemic actions in the bones, thus the serum calcium level remains low. This resistance is due to increase in 7-84 PTH fragments (caused by increased phosphate retention) which inhibit the action of the

whole hormone. Also, there is decreased density of PTH receptor on osteoblasts and there is increase level of circulating osteoprotegerin level (in uremia) that suppresses osteoclastogenesis by PTH. The numbers of vitamin D receptors and calcium sensors on the parathyroid gland are significantly decreased in advanced cases of renal failure.

Types of skeletal lesions of ROD:

Bone biopsy from the iliac crest is the gold standard for assessment of ROD. The following types of renal bony lesions are seen in CKD patients.

High Bone Turnover Disease: It is the result of high PTH found in patients with CKD. Excess PTH secretion increases osteoblastic and osteoclastic activities, leading to high rate of bone formation called, osteitis fibrosa. There is hugely elevated bone formation rate (2-4 times higher than normal), there is presence of fibrosis in the peritrabecular area and bone marrow. In milder cases, there is only moderate increase in bone formation rate but no such fibrosis.

Low Bone Turnover Diseases: In this type of bone lesion, there is usually low PTH level. There is impaired mineralization activity with decreased number of osteoblasts and osteoclasts. There is increased osteoid seam width surrounding the trabecular bone. Causes of low turnover disease include Osteomalacia and Adynamic Bone lesion, also called aplastic bone disease. In the past, the reason for adynamic bone lesion and low turnover disease was attributed to the frequent use of aluminium containing phosphate binders that causes low PTH secretion. But now aluminium containing phosphate binders are hardly used, but still ABD (adynamic bone disease) is being seen more frequently. This is probably because of use of high doses of hydroxylated vitamin D derivatives and calcium salts. This is seen more in CKD patients on peritoneal dialysis (high calcium in dialysis fluid). However, a new variant of adynamic bone lesion has been recently reported in patients on chronic hemodialysis.² The bone-forming pattern is similar to that of

ABD, but there is also increased osteoclastic bone resorption. However, the serum PTH level in this group of patients is low. Therefore, it is postulated, there maybe factors other than PTH, which activates osteoclastic activity in these patients. These toxic factors maybe uremic cytokins and α -microglobulin.

Mixed Type: In the mixed type of ROD, histologically there is osteitis fibrosa and osteomalacia and there is impaired mineralization. The serum PTH level is high.

Adult studies with bone biopsy reveal that the histological spectrum of ROD has changed tremendously over the last two decades. The therapeutic approach with large doses of calcium salts and hydroxylated vitamin D derivatives has resulted in more cases of adynamic bone disease. There are only few such studies of bone biopsy in children with advanced renal failure. As such, high bone turnover disease with secondary hyperparathyroidism remains the most common skeletal lesion of ROD in pediatric CKD patients. Yalcinkaya et al revealed in their studies that the incidence of high turnover bone disease was 47%, low turnover bone disease was 29% and the mixed type osteodystrophy was 24%.¹

Clinical Features of ROD and consequences of treatment failure:

Bone disease in CKD patients is usually asymptomatic. If there are symptoms, they appear late in the course of the disease. By the time symptoms appear, patients already have severe biochemical and histological bony consequences. Symptoms also depend on age of the patient and duration of the disease; infants may have features of rickets, while older children may have bony pain, peri-arthritis, genu vulgum, pathological fracture of long bones. Growth in CKD patients in children is already impaired by many factors (like anemia, acidosis, loss of appetite etc.); ROD may further affect the growth.^{3,4} Autopsy done on patients with osteitis fibrosa showed marked chondroclastic erosion and abnormal vascularization of growth plate cartilage. Adynamic bony lesions also inhibit growth by affecting endochondral bone formation. Studies have shown that high dose of calcitriol (more than 50 ng/kg/day) may actually impair the linear growth.

Two other syndromes are also seen to add further morbidity and ultimate mortality from ROD. They are coronary artery calcification and calciphylaxis. Calciphylaxis include both soft tissue and vascular calcifications. Both these syndromes are seen in ROD patients with high $\text{Ca} \times \text{PO}_4$ product ($\text{Ca} \times \text{PO}_4 > 70 \text{ mg/dl}$). These syndromes are still being evaluated and need further discussion elsewhere. In brief, the consequences of treatment failure for ROD can be summarized as follows:

- 1) Predisposes to soft tissue calcification that can be visceral, periarticular and most importantly cardiovascular.
- 2) Causes a significant positive $\text{Ca} + \text{PO}_4$ balance, thus increasing the morbidity and mortality of patients with end-stage renal disease.
- 3) Studies in adult CKD patients have shown that patients with serum $\text{PO}_4 > 6.5 \text{ mg/dl}$ and $\text{Ca} \times \text{PO}_4 > 72 \text{ mg/dl}$ have higher mortality than patients with serum $\text{PO}_4 < 6.5 \text{ mg/dl}$ and $\text{Ca} \times \text{PO}_4 < 52 \text{ mg/dl}$.

Ganesh et al have shown in their study on a large patient population on dialysis (>12,000 ESRD patients) that the patients with plasma $\text{PO}_4 > 6.5 \text{ mg/dl}$ have 56% higher mortality risk, mostly due to coronary artery disease and 27% have increased risk of sudden death. Furthermore, for each 10mg/dl increase in the $\text{Ca} \times \text{PO}_4$ product, there is an 11% increase in risk for sudden death.²

Ideal goals to achieve in the management of renal bone disease:

Considering all the consequences described above, the strategies for the management of ROD should include the following:

- 1) Prevention of parathyroid gland hyperplasia.
- 2) Optimize the serum PTH level in the range that ensures normal bone formation and corresponds with a normal rate of skeletal remodelling. PTH level should be kept in the normal range in predialysis patients and 2-3 times over upper normal limit in patients on dialysis.
- 3) Avoidance of positive balance of calcium x phosphate.
- 4) Therapy should start at the very early stage of CKD. When the creatinine clearance falls $< 60\text{-}70 \text{ ml/min/1.73 m}^2$, serum PTH starts to rise due to decrease level of calcitriol, so therapeutic intervention should be undertaken at this stage.
- 5) Excess dose of hydroxylated vitamin D may increase $\text{Ca} \times \text{PO}_4$ product (by increased gut absorption of them), thus predisposing to soft tissue calcification. Also it can cause adynamic bone disease, especially if given in pulses. Hence, excessive dose of hydroxylated vitamin D should be avoided and frequent monitoring is necessary for Ca , PO_4 , serum PTH and alkaline phosphatase.
- 6) Dietary PO_4 restriction is advisable, but associated protein restriction may not be good for growth in children and it is practically very difficult. However, most practitioners would advise to decrease phosphate intake

when the creatinine clearance falls below 50-ml/min/1.73 m². Phosphate restriction decreases serum PTH level and may help to maintain normal calcitriol level; however, there is already parathyroid gland hyperplasia when it is usually advised. So, early advice on dietary phosphate restriction to 800-1000 mg/day maybe useful.

Causes of therapeutic failure in the past:

Can be summarized as follows:

- 1) More importance was given in decreasing PTH secretion rather than preventing the growth of parathyroid hyperplasia. It is important to note that biological markers of SHPT (Secondary hyperparathyroidism) becomes abnormal late in the course of renal failure, by this time, significant nodular parathyroid hyperplasia is already present.
- 2) Introduction of vitamin D therapy in the late stage, when the serum PTH level was already 3-4 times higher than normal, that means high dose of such therapy was required which in turn resulted increase in Ca x PO₄ product.
- 3) Control of hyperphosphatemia and hypocalcemia was not considered so important.
- 4) Until recently, most of the phosphate binders contained Ca⁺⁺. Together with high dose of calcitriol (most commonly used vitamin D analog), it caused frequent episodes of hypercalcemia and in many instances, it predisposed to the development of adynamic bone disease.

New strategy for the treatment of ROD:

Prevention and treatment of ROD have always been great challenges for the nephrologists. From the discussion above, it is apparent that many consequences were unknown that we know now. Thus, it has become even more challenging now to especially prevent the occurrence of such consequences. We have, however, the following advantages in these days:

- 1) Better understanding of the disease process
- 2) Development of new drugs, like
 - (a) Calcium and aluminium free phosphate binders
 - (b) Paricalcitol, a non-hypercalcemic Vitamin D analogue
 - (c) Calcimimetics- e.g, cinacalcet HCL, which directly stimulate calcium sensing receptors and potentially suppress PTH secretion without increasing serum Ca⁺⁺.^{5,6}

With the use of newer drugs, strategies are being formulated at different renal centers. It is important to note that any such strategy must be created as an individual basis, the

factors need to be considered are age, type of primary disease, rate of progress of renal failure, nutrition, acidosis, dialysis or predialysis, type of dialysis and medication like steroid and growth hormone.

There may still some debates as to when to start treatment, however most nephrologists find it rational to initiate therapy at the early stage of CKD. Studies have found an increase in PTH secretion as creatine clearance falls to <60-70 ml/min/1.73 m². In addition, there is already a significant decrease in calcitriol level even at an early stage of CKD, which suggests that decrease in calcitriol level maybe a factor to cause secondary hyperparathyroidism. Thus, it may seem to be rational to start treatment at the early stage of CKD. However, the problem is that administration of calcitriol may result in an increase in the Ca x P burden. Dietary PO₄ restriction can normalize plasma calcitriol level and thus decrease serum PTH level. However, PO₄ restriction may not always be practical, especially in children; associated protein restriction may have deleterious effect on growth. In this situation, a new alternative vitamin D analog maybe very much useful. This analog is 'Paricalcitol (zemplar)', which has minimal effects on gut absorption of Ca and PO₄. It is an active analog based on vitamin D₂ structure (19-nor-1, 25-dihydroxy vit D₂) that suppresses PTH secretion but has minimal effect on serum level of Ca and PO₄. It is not a non-calcemic vitamin D, but has less calcemic effect. The result would be to correct secondary hyperparathyroidism while minimizing the toxicity resulting from increased level of Ca and PO₄.^{7,8}

A wide variety of vitamin D analogs were screened for the same purpose and in addition to paricalcitol, the other analogs used are

- 1) Doxercalciferol (Hecteryl) – a hydroxy vitamin D₂ that undergoes 25 hydroxylation in liver to form active 1-25 dihydroxy vit D₂.
- 2) 22-oxa-calcitriol (Moxacalcitol) -22-Oxacalcitriol (OCT) is a synthetic vitamin D analogue with less calcemic activity than calcitriol, and it effectively suppresses parathyroid hormone (PTH) secretion.

Among all these, the most commonly used vitamin D analog is paricalcitol. It is available in I.V. formulation for treatment of SHPT in dialysis patient and in capsule form for using in Stage 3 and Stage 4 CKD patients with SHPT. Studies have shown that the serum calcium enhancing pathways were activated most by calcitriol, slightly less by doxercalciferol and the least by paricalcitol.

Paricalcitol in CKD patients thus greatly diminishes the severity of SHPT and high bone turnover disease in new dialysis patients by controlling PTH and preventing

hyperplasia of parathyroid gland with minimal effect on calcium and phosphorus metabolism.⁹

Some nephrologists would like to initiate treatment for ROD with phosphate binders to decrease absorption of PO_4 and thus maintain normal serum phosphate level. This would suppress PTH secretion and would thus prevent the development of SHPT. However, the use of calcium containing phosphate binders (like calcium carbonate and calcium acetate) may lead to calcium overload and toxicity, together with calcitriol; it can further cause increased $\text{Ca} \times \text{P}$ burden, leading to the development of vascular and soft tissue calcification. 120 autopsy studies of children with chronic renal failure showed soft tissue calcification in 60% of patients and systemic calcification in 36%.³ Aluminium based phosphate binders also have detrimental effects on bones including adynamic bone disease.

Newer calcium free phosphate binders are thus useful and in demand at present. Sevelamer hydrochloride (Renagel) is the most common of such newly developed calcium free phosphate binders. Sevelamer has been shown to be effective in lowering serum phosphate, serum $\text{Ca} \times \text{P}$ product and PTH level, it also suppresses vascular calcification. The wider clinical use of Sevelamer is, however, limited by its high price. Currently, it is considered for patients with persistent hypercalcemia during calcium based binder therapy despite dose adjustment of vitamin D. The other two newly developed calcium free phosphate binders are Lanthanum carbonate (Fosrenol) and Ferric Citrate. Both have been shown to be effective in lowering serum phosphate level without increasing serum calcium. Ferric Citrate is slightly less effective in reducing serum phosphate. Long-term use of both these drugs would need further studies in future, since it is possible that both metals can accumulate in the bones. The other calcium and aluminium free phosphate binder is Magnesium carbonate (Magnabind), its use in pediatric patients is limited.¹⁰⁻¹²

Other agents to control SHPT and High Turnover Bone Disease:

Calcimimetics (Cinacalcet): Since 1993, there has been a new approach to decrease the secretion of serum PTH and thus control SHPT through the stimulation of calcium sensing receptors (CaSR) in the parathyroid gland. New agents were developed for the purpose, they are called calcimimetics as they mimic the effect of blood ionized Ca^{++} ; they lower the threshold of CaSR activation by extracellular Ca^{++} . The ultimate effect is decreased PTH secretion without an increase in serum calcium, phosphate or $\text{Ca} \times \text{P}$ product. The onset of action is very rapid, almost within minutes of administration. In some cases, few side effects were noted, one of which

was mild hypocalcemia. The calcimimetic agent used in adult patient is called AMG073, whose generic name is Cinacalcet. The drug has not been evaluated extensively in pediatric patients.

In future, this agent, by directly targeting CaSR in the parathyroid gland, may provide an alternative and/or adjunct to vitamin D therapy in ESRD patients with SHPT. The advantage is that it decreases PTH secretion without increasing serum calcium or worsening of the hyperphosphatemia. However, long-term studies are necessary for such therapy especially in pediatric patients because there is certain concern regarding its distribution in various tissues and its effects on their function. In this regard, a skeleton in growing children is very important since CaSRs are expressed in the epiphyseal plate of chondrocytes. However, the role of CaSR in the chondrocyte proliferation and differentiation is not yet clear.

Growth Hormone and ROD:

As a whole, the use of growth hormone in children with chronic renal failure remains controversial. It is known from animal models that growth hormone stimulates chondrocyte proliferation. Patients of CKD who receive growth hormone should be monitored for signs of ROD, slipped capital femoral epiphysis and avascular necrosis on serial radiographs, serum Ca , PO_4 , alkaline phosphatase and PTH levels should also be monitored. Long-term effects of growth hormone were studied in 45 pre-pubertal Dutch children with chronic renal insufficiency and no adverse effects related to PTH concentration or development of radiological of ROD were reported in that study.⁴

Parathyroidectomy in ROD:

Surgical excision of parathyroid gland is better than ethanol injection into the gland, but parathyroidectomy is rarely done nowadays as medical treatment of SHPT has improved significantly over the last decade. Current indications for parathyroidectomy are:^{13,14}

- 1) Severe episodes of hypercalcemia and hyperphosphatemia with high levels of serum PTH, not responding at all to medical treatment.
- 2) Recurrent bony fractures with severe ROD.
- 3) Extra skeletal calcification and calciphylaxis.

Conflict of Interest: None

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