39 *Newer Insights in Management of Renal Osteodystrophy*

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Abstract: Renal osteodystrophy (ROD) and abnormalities of mineral and bone are common complications of chronic kidney disease. Both high-turnover and low-turnover renal osteodystrophy occur due to an interplay of secondary hyperparathyroidism and 1α,25-dihydroxycholecalciferol (1α,25-dihydroxyvitamin D_3) deficiency. This realization, and that high Ca x P is associated with calcification of the lungs, cardiac and vascular tissues- major causes of mortality and morbidity in this group, has led to the development of treatment regimens that can maintain normal serum calcium and phosphate concentrations, reduce parathyroid hormone secretion, and correct a deficiency of 1α25-dihydroxycholecalciferol.

While bone biopsy is the gold standard for diagnosis of renal osteodystrophy, it is recommended for use in specific circumstances only, and serum biomarkers including iPTH, S. Ca, phosphorus and alkaline phosphatase are used more often to identify, assess and monitor treatment of renal osteodystrophy in CKD patients. A new era has emerged in phosphorus control with the emergence of non-calcium-non-aluminium binders Sevelamer and Lanthanum carbonate, and this class of drugs continues to proliferate rapidly. The evolution of second generation vit D compounds alfacalcidol and doxercalciferol, and recently paricalcitol has made it possible to suppress PTH while minimally affecting the mineral balance in intestine and bone. Calcimimetic agents are a newer modality for control of SHPT, and promise more precise control of serum PTH concentration and to help achieve the treatment targets while limiting skeletal and cardiovascular morbidity in patients with CKD. This article presents an insight into the newer developments in management of renal osteodystrophy while introducing the basic concepts in brief.

INTRODUCTION

Renal osteodystrophy (ROD), a disorder of bone remodeling, is a common complication of chronic kidney disease detectable in virtually all patients by the time 50% of renal function is lost.[1,2] Disturbances in mineral and bone metabolism are an important cause of morbidity, decreased quality of life, and extra-skeletal calcification in this group of patients and have been associated with increased cardiovascular mortality. While a definition for Renal Osteodystrophy was framed at the 2003 NKF conference, this definition failed to gain worldwide acceptance. Recently, an attempt was made to develop a clinically relevant, easily applicable definition and classification system for renal osteodystrophy at the second KDIGO Controversies Conference on 'Definition, Evaluation, and Classification of Renal Osteodystrophy' held in September 2005 at Madrid. Moreover, with the current proliferation of phosphate binders, Calcimimetics and development in vitamin D analogs, it has become imperative to keep abreast of the new trends in management of ROD.

PATHOGENESIS AND SPECTRUM OF RENAL OSTEODYSTROPHY

While the various clinical presentations of bone disease in CKD and their histological findings actually represent a spectrum, for clinical purposes they are often classified into three major histological groups:

1. Predominant hyperparathyroid bone disease
2. Low-turnover uremic osteodystrophy, encompassing osteomalacia and adynamic renal bone disease
3. Mixed uremic osteodystrophy consisting of mild to moderate hyperparathyroid bone disease and defective mineralization. It is worth reiterating that despite this classification, renal osteodystrophy should be considered a clinical spectrum, and transformation from one form to another can occur.

The mechanisms underlying ROD can be discussed under two headings: (1) high bone turnover renal osteodystrophy (Secondary Hyperparathyroidism), and (2) Low bone turnover renal osteodystrophy (Adynamic Bone and Osteomalacia). The mechanisms are summarized in Figure 39.1 and 39.2

Secondary hyperparathyroidism and 1α, 25-dihydroxycholecalciferol (1α, 25-dihydroxy-vitamin D_3) deficiency are identified as the major contributors to renal osteodystrophy (Fig. 39.1). This realization has led to the development of treatment regimens that can maintain normal serum calcium and phosphate concentrations, reduce parathyroid hormone secretion, and correct a deficiency of 1α,25-dihydroxycholecalciferol. These improvements in treatment have resulted in a decrease in the frequency and severity of osteitis fibrosa, the most common type of **renal osteodystrophy.**

Predominant Hyperparathyroid Bone Disease: Osteitis Fibrosa

Marrow fibrosis and increased resorption of bone consequent to an increase in number and activity of osteoclasts characterize this classic histological form of renal osteodystrophy, caused by secondary hyperparathyroidism. Bone formation is increased simultaneously, and is reflected by increased amounts of osteoid and nonlamellar bone.[3] In long bones, increased cortical resorption tends to reduce the bone mass, but in trabecular bone the accumulation of woven bone may leave the bone mass unchanged.[3] Thus, measurements of bone density do not correlate well with bone strength because of dystrophic mineralization and the accumulation of woven bone, which is much weaker than its lamellar counterpart.

Low Turnover Uremic Osteodystrophy: Osteomalacia

Osteomalacia is characterized by low rates of bone turnover, a mineralization defect, and an accumulation of unmineralized osteoid. The most common cause of osteomalacia is toxicity of aluminum and other heavy metals associated with the treatment of end-stage renal disease.[4] The incidence of osteomalacia has decreased with the elimination of aluminium exposure in patients[5,6] but the incomplete disappearance indicates that other factors, such as 25-hydroxycholecalciferol deficiency[7] are involved in this potentially devastating form of osteodystrophy. Osteomalacia associated with end-stage renal disease differs from that caused by vitamin D deficiency. The role of 1α, 25-dihydroxycholecalciferol deficiency in osteomalacia associated with end-stage renal disease is unclear and this form of osteodystrophy is generally refractory to treatment with vitamin D sterols.[8]

Low Turnover Uremic Osteodystrophy: Adynamic Bone Disease

This disease is most common in patients with end-stage renal disease without secondary hyperparathyroidism (e.g., after parathyroidectomy), who have been over treated with calcium

and vitamin D, or who have diabetes mellitus or aluminium intoxication. The association between CAPD and adynamic renal bone disease may be related to the greater transfer of calcium from the dialysate to the patient, and suppression of parathyroid hormone secretion that occurs with this form of dialysis as compared with hemodialysis.[9] 1α, 25-Dihydroxycholecalciferol also inhibits cell proliferation. This effect is important to consider in treating patients with well-controlled serum parathyroid hormone concentrations, because the use of 1α, 25-dihydroxycholecalciferol may promote the development of adynamic bone disease.[10]

Other Factors that may Affect Bone in CKD

Metabolic acidosis: Metabolic acidosis is common in advanced CKD and may affect bone by liberation of bone mineral as hydrogen ions are buffered by bone carbonate. In addition, acidosis may enhance osteoclast mediated bone resorption and inhibit osteoblast mediated bone formation.

Corticosteroids: Corticosteroids have a suppressive effect on bone formation and are associated with loss of bone and an increased risk of fracture. In the course of chronic renal disease, many patients might have received corticosteroid therapy and its use might complicate the manifestations of renal osteodystrophy.

Extra-skeletal Calcification: A Cause of Significant Mortality

Recently, there has been increasing evidence suggesting that disorders in mineral and bone metabolism associated with CKD are associated with increased risk for cardiovascular calcification, morbidity, and mortality.[11] The underlying mechanisms for this linkage are unclear but are probably related to an effect on vascular calcification (VC) leading to changes in cardiovascular structure and function.[12,13] Evaluation of extra-skeletal calcification therefore becomes an essential component in the work up and classification of the mineral and bone disorders in patients with CKD. KDIGO has recently attempted to incorporate all mineral and bone disorders associated with CKD under one classification system.

CLASSIFICATION OF ROD: A NEW VIEWPOINT (NKF-KDIGO 2005)

Keeping in view the significance of the evaluation of extra-skeletal calcification in patients with CKD, KDIGO has attempted to develop a clinically relevant classification system for renal osteodystrophy. The NKF-KDIGO controversy conference 2005 concluded that:

1. The term renal osteodystrophy be used exclusively to define alterations in bone morphology associated with CKD, which can be further assessed by histomorphometry, and the results reported based on a unified classification system that includes parameters of turnover, mineralization, and volume, and
2. The term CKD-Mineral and Bone Disorder (CKD-MBD) be used to describe a broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcification[14] (Fig. 39.3).

Renal Osteodystrophy: The New Definition and Description

The position statement defined renal osteodystrophy as an alteration of bone morphology in patients with CKD, which is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy. In order to clarify the interpretation of bone biopsy results in the evaluation of renal osteodystrophy, it was agreed to

use three key histologic descriptors—bone turnover, mineralization, and volume (TMV system)—with any combination of each of the descriptors possible in a given specimen (Fig. 39.3)

Chronic Kidney Disease—Mineral and Bone Disorder (CKD-MBD)

The position statement defined CKD-MBD as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of:

a. Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
b. Abnormalities in bone turnover, mineralization, volume, linear growth or strength, and
c. Vascular or other soft tissue calcification.

KDIGO has also proposed a framework for classifying CKD-MBD, dividing patients into four types based on the presence or absence of laboratory abnormalities (L), bone disease (B), and calcification of extra-skeletal tissue (C).[14] It was suggested that the use of the term "CKD-MBD" should be limited to disturbances caused by significantly reduced kidney function. While adult patients with a glomerular filtration rate of >60 ml/min/1.73 m^2 should be excluded, in pediatric patients, the level of glomerular filtration rate at which CKD-MBD abnormalities are detectable is higher (Glomerular filtration rate < 89 ml/min/1.73 m^2).

DIAGNOSIS

A battery of biochemical and hormonal tests is available to assess the derangements of calcium and bone metabolism in patients with CKD. The search for noninvasive serum or bone markers that predict bone turnover, mineralization status and bone aluminium accumulation has made available several indices, which though correlated with histological bone parameters, are still relatively poor predictors of the *type* of bone disease. At this time, bone biopsy performed after tetracycline labeling and processed undecalcified represents the most precise and accurate tool to assess renal osteodystrophy and aluminium accumulation in patients with renal disease.[15] However, the biochemical parameters are a fairly reliable means to identify high or low bone turnover states and to assess the severity of renal osteodystrophy, and bone biopsy is not recommended as part of a routine evaluation for ROD.

Role of Biochemical Markers

1. *Parathyroid hormone:* Serum PTH levels remain the best noninvasive indicator of bone turnover at this time. Parathyroid hormone measurements can be used to differentiate osteitis fibrosa or mixed disease from low turnover uremic osteodystrophy but are not sufficient to establish the type of osteodystrophy in an individual patient,[6,10] especially if calcitriol has been administered. It is also increasingly clear that in addition to 'intact' 84 amino acid PTH, most commonly utilized first-generation immunometric assays also detect other biologically active fragments of the hormone. These N-terminally truncated peptides appear to exert an inhibitory influence on bone cells and could be a contributory factor to perceived skeletal resistance to PTH.[16,17] Second-generation immunometric assays, more specific for 'whole' PTH (1-84) molecule, have been developed and are likely to attract increasing attention because of their superior reproducibility across sites.
2. *Total alkaline phosphatase:* While measurements of total alkaline phosphatase may provide an index of osteoblastic bone formation, there are several limitations to its interpretation. In addition to the dual origin of this enzyme (liver and bone), elevated serum alkaline phosphatase level can occur in patients with either high bone turnover state (e.g., hyperparathyroidism) or with low-turnover osteomalacia and rickets. Moreover, wide variations have been reported by studies examining the correlation of total alkaline phosphatase with PTH levels and histological parameters of bone turnover. However, total alkaline phosphatase level may be useful for monitoring the progression of bone disease and response to therapy.

3. *Bone specific alkaline phosphatase:* Preliminary studies in hemodialysis patients have demonstrated that bone-specific alkaline phosphatase is better correlated than PTH or total alkaline phosphatase with histomorphometric parameters of bone formation and resorption,[18] and may in future be helpful in diagnosis of both high and low turnover renal osteodystrophy especially when examined in conjunction with PTH levels.
4. *Serum calcium:* Serum calcium is an unreliable predictor of bone disease features in patients of CKD. While the total serum calcium concentration may decrease below normal in patients with advanced CKD, patients with hyperparathyroidism and adynamic uremic osteodystrophy may experience spontaneous or Vitamin D induced hypercalcemia during therapy. Nonetheless, it is important to monitor and control the calcium concentration during the course of CKD because it is a strong stimulus for PTH secretion. Although measurement of ionized calcium is the preferred method for evaluating serum calcium, total serum calcium concentration 'corrected' for albumin is used more often because of sample processing and cost involved in the assessment of the former.
5. *Serum phosphorus:* Generally, phosphorus concentrations do not indicate the severity or type of renal bone disease.[15] However, ensuring adequate phosphorus control is crucial because hyperphosphatemia may aggravate hyperparathyroidism by decreasing the levels of ionized calcium, decreasing the synthesis of calcitriol, and directly increasing PTH secretion.
6. *Other biomarkers:* Osteocalcin, an osteoblast product, is a good predictor of osteoblast number in bone and permits a distinction between the high and low turnover states of bone. However, serum levels of osteocalcin lack the sensitivity needed to distinguish mixed uremic osteodystrophy from other forms of renal bone disease.[15] Various breakdown products of type I collagen, including pyridinoline and deoxypyridinoline, have also been studied and could, eventually, play a larger diagnostic role as assays and interpretation are refined in relation to histology.

Frequency of Biochemical Tests

While in the past, low calcium levels or high phosphorus levels defined the need for parathyroid hormone (PTH) assessment, it is now recognized that many patients developing SHPT may have normal Ca and P lab results. Therefore, the new recommendations, as per the K/DOQI Clinical Practice Guidelines, are to monitor PTH levels on a regular basis in proportion to the stage of CKD: yearly in CKD stage 3 and quarterly in CKD stage 4 independent of Ca x P levels (Table 39.1). These measurements should be made more frequently if the patient is receiving concomitant therapy for the abnormalities in the serum levels of calcium, phosphorus or PTH, and in transplant recipients.[19]

Diagnosis of aluminium related bone disease: Although the above-mentioned biochemical measurements give information about bone turnover, formation and/or bone resorption, none directly indicates aluminium related bone changes. Tools used for diagnosis of aluminium related bone changes include:

1. Measurement of random serum aluminium levels
2. Deferoxamine infusion test (DFO test)
3. DFO test combined with measurements of serum PTH levels.

Though random serum aluminium levels have been correlated with stainable aluminium in bone, no threshold value has been determined to allow a clear-cut distinction between patients with and without aluminium-related bone disease.[15] The DFO test alone, or in combination with PTH measurement may be used as a screening test, however, because of large number of false-negative results,[15] bone biopsy remain the only reliable means of unequivocal diagnosis of aluminium deposition in bone.

Role of Bone Biopsy

As mentioned previously, histomorphometric analysis of bone is the gold standard for the diagnosis of renal osteodystrophy, although it is rarely preformed. Bone biopsies not only provide information on the type of renal osteodystrophy but they also allow tailored therapeutic measures in an individual patient. In selected patients with CKD, bone biopsy can be a valuable diagnostic tool in the evaluation and differential diagnosis of bone disease. The clinical indications for bone biopsy include, but are not limited to the following:[14]

- Inconsistencies among biochemical parameters that preclude a definitive interpretation
- Unexplained skeletal fracture or bone pain,
- Severe progressive vascular calcification (VC),
- Unexplained hypercalcemia,
- Suspicion of overload or toxicity from aluminium, and possibly other metals,
- Before parathyroidectomy if there has been significant exposure to aluminium in the past or if the results of biochemical determinations are not consistent with advanced secondary or tertiary hyperparathyroidism
- To be considered before beginning treatment with bisphosphonates.

Role of Imaging Techniques and Quantitative Measurement of Bone Mineral Content

At present, imaging plays only a minor role, with plain X-rays increasingly redundant in the diagnosis of osteodystrophy, though of increasing importance in the assessment of vascular calcification. Dual radiograph absorptiometry, quantitative ultrasonography, and quantitative computed tomography scanning are noninvasive methods used for the quantification of bone mineral density. Although several studies have shown that BMD measured at the distal radius site is predictive of fracture risk[20] and correlates well with PTH levels[21] in hemodialysis patients, its value in the evaluation of CKD-MBD still remains to be established. Some pilot studies have suggested that high-resolution MRI can provide detailed insight into the architectural implications of bone disease in CKD, but the method requires further validation in large scale studies.

MANAGEMENT OF ROD: A NEW PARADIGM

A new management paradigm for secondary hyperparathyroidism (SHPT) is emerging, with an emphasis on early identification and treatment of the disease. The prevention and treatment of renal osteodystrophy involves multiple issues and needs a multi-pronged approach, encompassing:

1. Prevention and treatment of hyperphosphatemia
2. Administration of calcitriol, vitamin D analogs, and/or calcimimetics to directly suppress the secretion of parathyroid hormone in patients with acquired calcitriol deficiency
3. Parathyroidectomy, in now infrequent patients with severe and refractory hyperparathyroidism.

Recently, NKF-K/DOQI has released guidelines for target concentrations for PTH, phosphorus and calcium in the various stages of CKD (Table 39.2).

Control of Serum Phosphorus

The clinical significance of hyperphosphatemia is illustrated by studies that have shown a direct correlation between serum phosphorus levels and death risk among dialysis patients. Lowrie and Lew[22] observed a significant increase in the risk of death in hemodialysis patients with serum phosphorus levels above 7 mg/dl, relative to patients in the reference range of 5 to 7 mg/dl.[23] Ca x P levels also increase as serum phosphorus increases, and high Ca x P is associated with calcification of the lungs and cardiac and vascular tissues,[24] key contributors to morbidity and mortality in patients with renal disease.

Dietary Restriction

Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated (> 4.6 mg/dL in Stages 3 and 4, and > 5.5 mg/dL in Stage 5 CKD).[25]

Phosphate Binders (Table 39.3)

Phosphate binders, the mainstay in the treatment of hyperphosphatemia, have evolved from the early use of aluminium gels to calcium salts, to novel, nonabsorbed, aluminium-free-calcium-free agents such as sevelamer hydrochloride and lanthanum carbonate.

Aluminium hydroxide. Aluminium hydroxide has become a cautionary tale in medicine because the metal was found to accumulate in the body and cause progressive and severe bone (osteomalacia) and brain disorders.[26,27] Current clinical practice guidelines advise that in patients with serum phosphorus levels >7.0 mg/dL, aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders.[25]

Calcium based phosphate binders. Both calcium-based phosphate binders and non-calcium, non-aluminum phosphate-binding agents are effective in lowering serum phosphorus levels. Still remaining a topic of debate, current guidelines recommend either may be used as the primary therapy.[28] However, calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of >10.2 mg/dl), or whose plasma PTH levels are < 150 pg/ml on two consecutive measurements.[28] While according to K/DOQI guidelines the serum calcium-phosphorus product should be maintained at < 55 mg^2/dL^2,[25] elevations beyond this value are common with calcium-based binders. Moreover, calcium-based binders are frequently not well tolerated, and patient adherence is poor.

New Approaches: Calcium-free, Aluminium-free Phosphate Binders

Sevelamer hydrochloride. Sevelamer is a hydrogel that is completely resistant to digestive degradation. In phase III studies in hemodialysis patients, sevelamer treatment decreased serum phosphorous to similar levels as compared to calcium acetate. Only 5% patients taking sevelamer experienced hypercalcaemia (> 11.0 mg/dl) as compared with 22% of patients receiving calcium acetate ($P < 0.0001$).[29] In addition, the drug was also found to have a beneficial effect by binding bile salts and reducing LDL cholesterol.[30,31] In a recent prospective randomized clinical trial sevelamer hydrochloride also slowed the progression of cardiovascular calcification.[32]

Sevelamer or calcium acetate: A comparison. Studies comparing calcium acetate and Sevelamer found that the calcium salt controlled phosphorus more effectively, and was more likely to produce acceptable phosphorus levels.[31] As expected, the calcium levels were significantly higher with calcium acetate, but because of a greater degree of phosphorus reduction, calcium acetate therapy reduced the calcium-phosphorus product below the level achieved with Sevelamer.[31] Another study reported that coronary and aortic calcification, progressed more rapidly in the calcium treated group.[32] Thus, a debate on the superiority of sevelamer or calcium continues. On one hand is argument that calcium binders, inevitably lead to positive calcium balance; on the other hand, calcium's purported greater effectiveness compared to sevelamer may outweigh any potential adverse clinical consequences of calcium accumulation. What is the answer?

Lanthanum carbonate. Lanthanum Carbonate is an effective non-calcium-non-aluminium phosphate binder recently approved by FDA. Serum phosphate control with lanthanum carbonate is similar to that seen with calcium carbonate but with a significantly reduced incidence of hypercalcemia. Lanthanum carbonate is well tolerated and may be more effective in reducing calcium x phosphate product than calcium carbonate.[33,34] A change to lanthanum

carbonate from other phosphate binder therapies provides continued mean serum phosphorus control for ESRD patients with hyperphosphatemia, while significantly reducing their required daily dose of phosphate binder.[35]

Future Trends in Management of Hyperphosphatemia

Emerging phosphate binders

Polynuclear iron preparations: The solubility product of Polynuclear Iron Preparations and phosphate is extremely low. While small-scale human trials have suggested their efficacy and tolerability, they are in the early stages of clinical development at this time. Zerenex^{TM}, an oral, inorganic, iron-based phosphate binder is currently in Phase II clinical development. In two previous phase II clinical trials, Zerenex^{TM} was able to significantly reduce serum phosphorous ($p < 0.005$) comparable to calcium-based products. Although no human studies have been published, Zirconyl chloride octahydrate *(ZCO)* was compared with aluminium and found to be of equivalent potency in animal studies besides being completely unabsorbable and, therefore, unlikely to be toxic.[36] *ILY-101* is a novel; metal-free, non-absorbed polymeric phosphate binder developed for the treatment of hyperphosphatemia and is currently under clinical trials.

Na-phosphate transport inhibitor. Niceritrol is a nicotinic acid prodrug, is found to inhibit sodium phosphate co-transporter in the small intestine in rodents[37] increasing fecal phosphate excretion. It has shown some efficacy in a small human trial[38] and is currently under study.

Dialysis: Emerging Trends. Substantial amounts of phosphorus are removed with continuous ambulatory peritoneal dialysis but not to an extent that precludes use of phosphorus binders.[39] The intermittent nature of conventional hemodialysis (3 treatments/ week) is also insufficient to prevent overall positive phosphorus balance.[40,41] Intermittent *hemo-diafiltration*,[42] Short daily hemodialysis and nocturnal hemodialysis have shown improved phosphorus control in patients of CKD. During a 4-yr observational study that compared patients receiving NH, conventional intermittent hemodialysis, and short daily hemodialysis, only NH showed a significant reduction in the serum phosphorus levels and eliminated the need for phosphate binders.[43-45] NH has also been associated with improved solute clearance, quality of life, BP control, and reduction in medication requirements.[46] However, obstacles to its use on a larger scale include unfamiliarity with home hemodialysis as well as the cost of equipment.

Management of Calcium

Dietary Calcium Supplements

Patients with advanced CKD frequently require oral calcium supplementation because of a combination of impaired calcium absorption and suboptimal dietary quantities of calcium. The calcium supplements should be prescribed in several small doses throughout the day, and ingestion of calcium supplements with meals that are rich in phosphate should be limited if the goal is to augment intestinal absorption of calcium rather than to bind phosphorus in the intestine. Calcium should be given cautiously to patients with marked hyperphosphatemia because of the risk of increasing the Ca x P and predisposing the patient to extraskeletal and cardiovascular calcifications. Monitoring in these patients should also be more frequent (biweekly or monthly) because of the variability in response of individual patient to a given amount of calcium.

Dialysate Calcium Levels

The level of calcium in dialysate fluid can affect serum calcium levels in patients treated with maintenance hemodialysis. While in the past, a dialysate calcium of 3 to 3.5 mEq/L was recommended for patients ingesting aluminium containing phosphate binders, with the advent of

newer calcium based phosphate binders, this level has seen a lowering and now a dialysate containing 2.5 mEq/L of calcium is the standard of care (18). Lower calcium concentrations (1.5 to 2 mEq/L) may be indicated in patients with overt hypercalcemia or adynamic bone disease with a suppressed intact PTH level (< 100 pg/ml). However, this course of action mandates close follow up of intact PTH and serum calcium levels and an aggressive search for the underlying cause of the hypercalcemia.

Role of Calcitriol and Vitamin D Analogs

The old treatment paradigm for treatment of ROD was to utilize dietary phosphorus restriction, Ca-based Phosphate binders and Ca supplements, and only limited amounts of active vitamin D were prescribed. This was primarily because of the risks of elevation in Ca, P, and urinary Ca with its attendant risk of renal calcification that was associated with use of the first-generation vitamin D agent- calcitriol. The new treatment paradigm is based on the recognition that active vitamin D is crucial to maintain and re-establish patient's bone health, and recent evidence that active vitamin D may also be important for cardiovascular health. The concept behind the development of vitamin D analogs as therapy for SHPT was to retain the beneficial actions of Vit D on the parathyroid, but minimize the effects on mineral balance in intestine and bone. Structural analogs of active vitamin D have been developed that have demonstrated less effect on Ca and P balance, and these can be safely used at higher doses than calcitriol.

Over the last four decades, Vitamin D agents have evolved from calcitriol to the second generation compounds alfacalcidol (1-alpha (OH) D3) and doxercalciferol, (1-alpha (OH) D2), and in 1985 paricalcitol was synthesized. Paricalcitol has a differential tissue activity and is therefore called a selective analog or selective vitamin D receptor activator (SVDRA). Recently, a large cohort study suggested a possible survival advantage for those patients treated with paricalcitol.[47] Intravenous paricalcitol and oral 1α(OH) D2 (doxercalciferol) have been approved for use in the United States while oxacalcitriol (OCT) is currently under review. The mechanisms by which these analogs exert their selective actions on the parathyroid glands are under investigation and knowledge of this may allow the design of more effective analogs in the future[48] (Table 39.4).

Calcimimetics: Newer Modality to Suppress PTH

Cinacalcet hydrochloride and NPS R-568 are allosteric modulators of the calcium receptors on parathyroid, enhancing its sensitivity to ambient calcium and thereby countering the under-expression of the parathyroid calcium receptors and partial loss of calcium-driven PTH suppression. Cinacalcet has recently been approved for the treatment of SHPT in dialysis patients. In addition to reducing PTH levels, serum calcium, phosphorus, and consequently calcium x phosphorus levels also decline with the use of cinacalcet.[49\51] The respective roles of calcitriol and cinacalcet as therapy for SHPT are determined not solely by the serum concentration of PTH, but also by the prevailing calcium, phosphate and Ca × P. In circumstances where calcium and Ca × P are low, treatment would typically start with calcitriol. Cinacalcet would be favored as initial therapy when calcium or Ca × P are high. Calcimimetic agents can enable more precise control of serum PTH concentration and help achieve the treatment targets while also limiting skeletal and cardiovascular morbidity in patients with CKD.

Control of Metabolic Acidosis

Chronic metabolic acidosis, a characteristic of stage IV and V of CKD, is also implicated in the loss of bone mineral. Although the clinical data are not conclusive, K/DOQI guidelines suggest that total CO_2 should be maintained at >22 mmol/L to prevent bone demineralization,[19] and serum levels of total CO_2 should be monitored more often in these patients. Exogenous alkali

salts containing citrate can increase the absorption of dietary aluminium in patients with CKD and therefore should be avoided in patients who are exposed to aluminium salts.

Parathyroidectomy: For Refractory Hyperparathyroidism

While calcitriol can decrease the PTH synthesis per cell through the powerful suppression of PTH gene transcription, its ability to influence parathyroid hyperplasia is more limited. Early on, calcitriol can inhibit cell proliferation both directly and through increasing serum calcium concentrations, but later stages of clonal proliferation of parathyroid cells are associated with reduced expression of both vitamin D and calcium-sensing receptors (CaR), and SHPT becomes refractory to treatment. Although calcimimetic agents have been shown to prevent parathyroid proliferation in animal studies,[52] their effect in long-term human disease remains to be seen. Thus, current treatment guidelines suggest surgical parathyroidectomy as the sole treatment for significant parathyroid hyperplasia.

APPROACH TO TREATMENT OF RENAL OSTEODYSTROPHY

Although the treatment modalities for management of ROD have proliferated in recent decades, the approach and best treatment still remains conjectural and far from perfect. The following figures depict an approach to management of renal osteodystrophy as suggested by the latest K/DOQI guidelines (Figs 39.4 to 7).[19]

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