CHAPTER **41**

RENAL OSTEODYSTROPHY, A SUBSET OF CHRONIC KIDNEY DISEASE-MINERAL BONE DISORDER

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This article is a synopsis of an article published in *Southern Medical Journal*, 2012 by Chauhan et al entitled "Current Concepts and Management Strategies in Chronic Kidney Disease – Mineral Bone Disorder: Review article." During our literature review we found this article was recent, apropos, and succinct. In their article, they publish their search strategy listing all keywords used.

The term renal osteodystrophy (ROD) is now reserved to describe one component of a broader disease process. In 2006 the National Kidney Foundation position paper stated that ROD refers only to the changes in bone seen in a wider disease process that also encompasses endocrine, mineral, bone, and calcific vascular disease, chronic kidney disease (1). Since 2009 the term chronic kidney disease–mineral bone disorder (CKD-MBD) was coined by the Kidney Disease Improving Global Outcomes foundation (KDIGO) (2). Bone mineral changes can occur early in the progression of chronic kidney disease (CKD) with changes in parathyroid hormone levels as early as stage two CKD (3). Although the changes seen in the vascular tree with calcification of vessels, especially the coronary arteries, are not emphasized, they are the most important sequelae seen in CKD-BMD (4, 5).

Glomerular filtration rates in ml/min/1.73m^2 for each stage of chronic kidney disease per the National Kidney Foundation are Stage 1: slightly decreased GFR at <90, Stage 2: 60-89, Stage 3: 30-59, Stage 4: 15-29, Stage 5: <15. The rate of CKD in the US is estimated at just over 15% (6). One retrospective study evaluated rates of hypertension (87%), diabetes (35%), cardiovascular (40%) and peripheral vascular disease (14%) in predialysis CKD (7). Interestingly these rates are similar in the dialysis patient population (6). Patients with predialysis CKD have a 56% higher mortality rate and this number increases with lowering GFR. This level increases to 6.5 to 7.4 times greater mortality rates when patients end up requiring dialysis (6). Notable is that cardiovascular disease is the greatest cause of death. Relative to CKD-MBD it is approximated that roughly 10% of the US population has or likely has the beginnings of the disease process. Again, changes can begin as early as Stage II (3). CKD-MBD leads to both medial and intimal calcification of the coronary arteries especially in the subset of patients predisposed with co-morbidities and other risk factors (4).

BONE DISEASE

There are varying responses to the decreased kidney function in terms of the bone mineral changes from high turnover of osteitis fibrosa cystic and the low turnover rates in dynamic bone disease and osteomalacia and it is possible to see the full range in one patient. With osteitis fibrosa cycstica there is an increase in parathyroid hormone (PTH) with GFR <70 ml/min/1.73m^2 (3). The stimulus for the increase in PTH secretion includes phosphate retention. As a response to phosphate retention, PTH secretion increases, thereby normalizing phosphate levels. Hence increased PTH is a better marker than phosphate levels in early CKD (8). In fact phosphate levels may not elevate until GFR is as low as 20 ml/min/1.73m^2 (9). As the GFR decreases, phosphate is retained and binds with the free calcium decreasing its level. Simultaneously the decrease in kidney function prevents the conversion of vitamin D to its active form calcitriol, resulting in less calcium absorption and a decrease in the negative feedback that calcitriol has on the parathyroid gland (10, 11). Third, fibroblast growth factor-23 (FGF-23) is secreted by osteocytes in response to elevated phosphate levels and also decreases the formation of calcitriol by blocking the formation at the enzymatic level namely 1-alpha-hydroxylase (12). High levels of FGF-23 have also been linked to increased mortality rates and cardiovascular events in both CKD and the general population (13, 14). Low vitamin D leads to decreased calcium absorption and loss of inhibition on the parathyroid gland (10). This all leads to decreased calcium in turn stimulating secretion of PTH. This increases phosphate filtering by the kidneys and drops phosphate levels to normal levels. Lastly, the increase in phosphate also causes direct increases of PTH secondary to gene expression on the gland. Paradoxically, elevated PTH is a better marker for early CKD because of the rebound effect in normalizing the phosphate levels.

The calcium sensing receptors located on the parathyroid function in a negative feedback manner. The decrease in calcium from calcium-phosphate binding and diminished calcitriol results in reduced negative feedback (15). The parathyroid gland can hypertrophy and the number of calcium receptors in the new tissue is reduced (16). Under these conditions PTH secretion can progress at high levels even with normal or normalized calcium levels. The PTH receptors on bone can also become resistant over time leading to again increased PTH levels (17).

Tertiary hyperparathyroidism occurs when the parathyroid becomes hyperplastic and no longer responds to the calcium negative feedback (18). If this continues the parathyroid can become a primary nodular tumor that never reduces in size or activity even if calcium levels are normalized.

With increased PTH, the bone turnover is high and extraosseous calcifications can occur in all tissues including the arteries (19). Over time a cycle occurs where PTH continues to increase phosphate release from bone making the hyperphosphatemia worse (20).

In adynamic bone disease there is decreased bone turnover and collagen synthesis. This typically occurs later on in pre-dialysis CKD or end-stage renal disease (ESRD) often seen in diabetes (21, 22). Over-suppression of PTH is the mechanism that causes this syndrome. It occurs secondary to the use of calcium based phosphate binders and vitamin D analog supplementation. Other factors include diabetes, older age, and aluminum (23, 24). These patients can be asymptomatic or suffer hip and other fractures and have hypercalcemia (24). A review of hip fractures in the CKD population revealed that a PTH level of less than 195 pg/dL predicted a high risk of fracture (25). The Kidney Disease Outcomes Quality Initiative (K/DOQI) reports a four-fold increase in hip fractures in the dialysis population (26). There is a lack of uptake or release of calcium from bone and any calcium intake causes hypercalcemia. This leads to increased cardiovascular calcifications and complications (26).

Osteomalacia has low bone turnover but increased amount of under mineralized collagen. The primary cause of osteomalacia was aluminum toxicity secondary to aluminum-based antacids to bind phosphate. This practice has been solved with improved dialysis treatment and elimination of aluminum (26).

In 2009, the KDIGO guidelines suggested serum calcium, phosphate and PTH should all be checked at intervals based on the CKD stage. Absolute PTH levels are not as important as upward trending and maintained high levels of PTH. The evidence for treating elevated PTH is weak since it has not shown to decrease the sequelae seen with CKD. It is recommended that both calcium and phosphate be kept in the normal range based on their individual levels in lieu of the old model of the calcium-phosphate product levels (27). Vitamin D levels should also be checked once a year (2). Of note is that these guidelines are based primarily on expert opinion not clinical studies. The recommendation is to base treatment on trends in values and not individual data points.

The diagnosis of the type of bone disease seen with renal osteodystrophy is not possible without a bone biopsy to evaluate the morphology directly. This is not often done but under some circumstances may be recommended and the source is typically the iliac bone crest. Bone specific alkaline phosphatase or intact PTH can be used to help determine the level of bone turnover in lieu of the bone biopsy (2). Bone mineral density or radiographs are not recommended for the evaluation of bone disease in CKD (26). Radiographs are not reliable and BMD has not been shown to predict fracture rates in the CKD population as it does in the general population (2).

Although KDIGO does not recommend routine screening for vascular calcifications, when evaluating for it, the recommended tests are a lateral lumbar radiograph and echocardiography. CT may be recommended when calcifications are present and the level of involvement needs to be assessed. When vascular calcifications are present there is a high risk for cardiovascular events (2).

TREATMENT

The goal of treatment of CKD-MBD is to maintain normalized calcium and phosphate levels. When PTH is rising or stays above the normal limit patients should be evaluated for hyocalcemia, hyperphosphatemia, and vitamin D deficiency (2).

High turnover osteodystrophy is treated by preventing the high phosphate levels even though there is not significant evidence to support it (2). Using the elevated PTH as the marker, the phosphate levels are checked. When phosphate is elevated, dietary restriction to about 800 to 1,000 mg/day is initiated (26). Protein sources with minimal phosphate are recommended such as meat and eggs. If this fails after four months, depending on the corresponding calcium levels either a calcium or a non-calcium based phosphate binder is administered (2). If vitamin D deficiency is present (<30 ng/ml) it is treated initially with ergocalciferol as long as calcium is not above normal. If after six months PTH is not normalized, then oral vitamin D analog can be added as long as the calcium does not exceed 9.5 mg/dl or if phosphate is elevated. When this fails a calcimemetic such as cinacalcet

can be added but is reserved for dialysis patients since there are no data in pre-dialysis CKD. Severe cases may require partial parathryoidectomy (2).

Adynamic bone disease is marked by low PTH levels. Although no trials have been undertaken to evaluate treatment there is evidence that this disease is not benign. Levels of PTH below 11 pmol/L (100 pg/ml) are used as the decision point for adynamic bone disease. Bone biopsy is not often performed but treated empirically by allowing the PTH levels to increase. This permits increased bone turnover and is achieved by decreasing the negative feedback on the parathyroid. Calcium phosphate binders and vitamin D is reduced or eliminated and the PTH level monitored and allowed to increase to normal levels. Low PTH is also found in the general population diagnosed with osteoporosis and is now being used to treat it (2).

Vascular calcifications are treated with optimal control of PTH, calcium, phosphate, and vitamin D levels. The role of cinacalcet is currently under investigation for this indication since it is very effective at controlling recalcitrant cases (28). Other therapies include statins, calcium-channel blockers, and subtotal parathyroidectomy (29-31).

CONCLUSION

CKD-MBD compromises bone health and the vascular tree leading to increased morbidity and mortality. The objective of treatment is to evaluate and normalize calcium, phosphate, PTH and vitamin D, especially in the case of vascular calcifications. In high turnover bone disease the goal is to control phosphate levels. Allowing PTH to elevate is the goal in adynamic disesase.

As podiatrists, our role is to understand the underlying disease process and factor it in to our decision making and treatment decisions. The ESRD patient requiring dialysis has always been understood to be a high-risk population. It is important to factor in bone health in early renal disease especially when recommending any procedures that will require bone healing. This subset of patients is often diabetic, focused on their primary disease process, and may not fully understand their current renal status. We need to be good stewards of their overall health and help them make educated decisions by identifying and factoring in early CKD-MBD when present.

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