The Consequences of Uncontrolled Secondary Hyperparathyroidism and Its Treatment in Chronic Kidney Disease

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ABSTRACT

Secondary hyperparathyroidism (HPT) is a common complication of chronic kidney disease (CKD) and a frequent cause of clinically significant bone disease. Soft-tissue and vascular calcification, cardiovascular disease, and calcific uremic arteriolopathy (CUA) are additional serious consequences of the disorder that may contribute directly to cardiovascular morbidity and mortality in patients with CKD. Less widely appreciated manifestations include neurological disturbances, hematological abnormalities, and endocrine dysfunction.

Secondary HPT arises from alterations in calcium, phosphorus, and vitamin D metabolism that develop early in the course of CKD and become more pronounced as kidney function declines. Treatment is often delayed, however, until the disease is well established. Current therapeutic strategies rely largely on the use of vitamin D sterols to diminish excess parathyroid hormone (PTH) synthesis and to lower serum or plasma PTH levels, but their use is often confounded by increases in serum calcium and phosphorus concentrations, changes that can aggravate soft-tissue and vascular calcification. As such, there is a need for new therapeutic interventions that can effectively lower serum or plasma PTH levels without producing untoward side effects.

The current review summarizes the diverse manifestations of secondary HPT in patients with CKD. The consequences of inadequately controlled secondary HPT and the adverse effects of selected therapeutic interventions for the disorder on vascular calcification and cardiovascular disease in those with CKD are discussed.

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD) (1,2). It arises predominantly from disturbances in calcium, phosphorus, and vitamin D metabolism that emerge as kidney function declines. Collectively these changes contribute to excess parathyroid hormone (PTH) synthesis and secretion, to the development of parathyroid gland hyperplasia, and to the persistently elevated circulating levels of PTH that characterize the disorder.

The preeminent consequence of SHPT is metabolic bone disease, which is a frequent cause of pain and disability among patients with stage 5 CKD who are treated with dialysis (3,4). Features include reductions in bone mass, alterations in the microarchitecture of bone, and skeletal fractures (5,6). Indeed, the treatment of SHPT and efforts to control excess PTH secretion are undertaken primarily to prevent or attenuate the detrimental effects of persistently high serum or plasma PTH levels on bone metabolism and skeletal integrity.

It has been known for many years, however, that the adverse effects of SHPT are not confined to the musculoskeletal system (7). Marked impairments in kidney function ultimately cause phosphorus retention and hyperphosphatemia, changes that contribute to elevated PTH levels. Either alone or together with the interventions designed to manage them, hyperphosphatemia and persistently high PTH levels lead to serious extraosseous complications, including vascular calcification (8,9). The extraskeletal manifestations of SHPT have received considerable attention recently as potential nontraditional risk factors for cardiovascular morbidity and mortality in patients undergoing long-term dialysis (10).

Other nonskeletal consequences of SHPT include soft-tissue calcification and possibly calcific uremic arteriolopathy (CUA), which is also known as calciphylaxis (11). Abnormalities in endocrine function, impaired erythropoiesis, and neurologic disturbances also occur (7,12).

Because SHPT develops relatively early during the course of progressive CKD, plasma PTH levels are often substantially elevated in patients with stage 3 or stage 4 CKD, even when serum calcium and phosphorus levels are within the normal range (13). Many patients with CKD thus have histologic evidence of renal bone disease long before regular dialysis is required to manage advanced kidney failure (14). Recent observations provide additional evidence that abnormalities in bone and mineral metabolism are common and can be detected readily when appropriate biochemical assessments are

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done relatively early in the clinical course of CKD. The detrimental impact of SHPT on the skeleton during the course of progressive CKD probably accounts for substantial reductions in bone mass in those first starting renal replacement therapy, changes that affect cortical bone most prominently (15). The potential for adverse clinical outcomes from inadequately controlled SHPT is thus present throughout the continuum of CKD.

This review examines various consequences of inadequately controlled SHPT not only in patients with stage 5 CKD undergoing treatment with dialysis, but also in those with less advanced CKD. The benefits and risks associated with specific therapeutic interventions are also discussed.

Clinical Complications of SHPT

Skeletal Complications

The adverse effects of SHPT on the skeleton are well documented and they have been reviewed in some detail (16). Manifestations include bone pain, particularly when standing or bearing weight, periarticular pain, and joint stiffness. These features cause substantial disability in many patients with CKD, particularly if muscle pain and weakness also occur (17). The capacity to ambulate or to engage in various physical activities can be markedly impaired.

The risk of skeletal fracture is greater by far in patients undergoing long-term dialysis than in persons from the general population (6). The disparity in fracture rates is greatest in the youngest age groups (6). The incidence of hip fracture was thus more than 85 times higher among dialysis patients under 45 years of age than in healthy subjects of the same age (6). Bone fractures, particularly hip fractures, are associated with substantial morbidity and can result in death (16).

In some studies, bone mass, which is an important determinant of fracture risk in the general population, has been related inversely to serum or plasma PTH levels in patients with CKD (15). This has not, however, been a consistent finding. The severity of SHPT is thus probably only one of many factors that adversely affect bone mass in such patients.

Effects of PTH on Bone Metabolism

Available data indicate that PTH is the major regulator of bone remodeling and skeletal turnover in patients with CKD (18). Parathyroid hormone promotes the recruitment and differentiation of osteoclasts, cells primarily responsible for the dissolution of bone mineral and for the degradation of bone collagen during bone resorption (19,20). High circulating levels of PTH increase both the number and activity of osteoclasts and enhance active, cell-mediated bone resorption (21).

Because osteoclasts do not express receptors for PTH, many of the actions of PTH on osteoclasts are mediated indirectly through the release of various cytokines and growth factors from osteoblasts and other cells within the microenvironment of bone and adjacent bone marrow (20). The recent identification of osteoprotegerin (OPG), together with receptor activator of NF-κB (RANK) and RANK ligand (RANK-L), provides important new insights into the molecular signaling that accounts for the close coordination of osteoclast-mediated bone resorption and osteoblast-mediated bone formation during skeletal remodeling (22). This pathway is integrally involved in the recruitment and differentiation of osteoclasts, and the levels of expression of RANK, RANK-L, and OPG are affected by several hormones and cytokines that serve as important modulators of bone metabolism (22). It is anticipated that future work will clarify the role of this pathway in the regulation of skeletal remodeling in patients with SHPT due to CKD (23,24).

Apart from its effects on bone resorption, PTH promotes bone formation via direct actions on osteoblasts, which abundantly express receptors for PTH (18). Both the number and activity of osteoblasts increase as PTH concentrations increase (25). These cells synthesize type I collagen and are responsible for its subsequent extrusion into the extracellular space to form a collagenous bone matrix. Osteoblasts also participate in the mineralization of bone collagen to form fully calcified skeletal tissue.

High-Turnover Bone Disease

Because PTH enhances both osteoblastic and osteoclastic activity, bone formation and resorption increase in a coordinated manner as PTH levels rise. High rates of bone formation result in the deposition of woven bone, which is structurally inferior to lamellar bone due to abnormalities in the spatial arrangement of collagen fibrils. As a result, the material strength of skeletal tissue may be diminished and its structural integrity compromised when bone formation and turnover are substantially elevated. Such changes are an integral component of the high-turnover skeletal lesions that characterize patients with SHPT (2).

In patients with mild to moderate SHPT, bone formation is greater than normal and the number of osteoblasts and osteoclasts are increased, but there is no evidence of peritrabecular or marrow fibrosis (21). In contrast, greater increases in osteoblastic and osteoclastic activity and high rates of bone formation are seen in those with more advanced SHPT, and fibrous tissue accumulates within the marrow space and adjacent to bony trabeculae. In severely affected individuals, marrow fibrosis is a prominent finding, accounting for the histopathologic term osteitis fibrosa cystica. Fibrous tissue accumulation within the marrow space can displace normal blood-forming elements and aggravate the anemia associated with CKD.

The localized deposition of fibrous tissue in cancellous bone may partially replace existing trabecular structures and compromise structural integrity. Similar changes can affect cortical bone and lower the threshold for skeletal fracture. Indeed, extensive fibrous tissue accumulation immediately adjacent to the epiphyseal growth plate can result in slippage and displacement of femoral epiphyses in children and adolescents with CKD (26).

Two to three decades ago, high-turnover lesions of renal osteodystrophy were found in the majority of

patients undergoing dialysis (27). Osteomalacia, arising from defects in skeletal mineralization, was also fairly common before the vitamin D sterol, calcitriol, became widely available for clinical use. The osteomalacic form of renal bone disease was often attributed to persistent hypocalcemia or, less frequently, to persistent hypophosphatemia in patients with CKD. Bone aluminum accumulation and aluminum toxicity were subsequently recognized, however, as major causes of the disorder in those treated with long-term dialysis.

The term mixed renal osteodystrophy describes the combined histologic features of osteitis fibrosa cystica and osteomalacia of varying severity (27). Bone formation and turnover may be high, normal, or low in patients with mixed skeletal lesions depending upon the extent of the mineralization defect attributable to the osteomalacic component of the disorder (28). Mixed renal osteodystrophy is encountered somewhat less often in contemporary clinical practice, a change probably due to the use of large oral doses of calcium as a phosphate-binding agent and to the widespread use of vitamin D sterols to treat SHPT (3). These agents may, however, lead to other complications in patients with CKD, as discussed subsequently.

Low-Turnover Bone Disease

Low-turnover skeletal lesions, particularly the adynamic lesion of renal osteodystrophy, represent the other end of the spectrum of renal bone disease (25,29). Both osteoblastic and osteoclastic activity are reduced, and the rates of bone formation and turnover are subnormal.

Adynamic bone is not itself a manifestation of SHPT, but the disorder often arises after the treatment of SHPT with vitamin D sterols, particularly large intermittent doses of calcitriol (30). Calcitriol may exert direct inhibitory actions on bone cells apart from those mediated indirectly by lowered circulating PTH levels (30). These include reductions in the recruitment of mature osteoblasts from precursor cells and inhibitory effects on differentiated osteoblastic function, such as decreases in collagen synthesis. The concurrent administration of large oral doses of calcium as a phosphate-binding agent probably enhances the suppressive effects of vitamin D therapy on bone formation by promoting intestinal calcium absorption and raising serum calcium levels, changes that further lower PTH levels (31).

Adynamic bone is more common in patients treated with peritoneal dialysis (PD) than in those undergoing hemodialysis (HD), accounting for approximately two-thirds of skeletal lesions as documented by bone biopsy (3). This finding may reflect the sustained uptake of calcium into plasma during prolonged exposures to calcium-containing PD solutions.

Risks associated with adynamic bone in patients with ESRD include skeletal fracture and hypercalcemia (32,33). Indeed, serum calcium concentrations are higher, on average, in patients with adynamic bone than in those with high-turnover skeletal lesions, and episodes of hypercalcemia occur more often (34). These biochemical disturbances may promote or facilitate the deposition of calcium and phosphorus in soft tissues, aggravate the extent of vascular calcification, and increase the risk of CUA. Data are not yet available, however, comparing the prevalence of soft tissue and/or vascular calcification between patients with adynamic renal osteodystrophy and those with SHPT.

Nonskeletal Complications

Soft tissue calcification has been recognized for many years as a common and potentially serious complication of kidney failure (7). Elevated serum phosphorus levels have been shown consistently to represent an important risk factor for soft tissue calcification. This was the case many years ago when high-turnover bone lesions were the predominant type of renal osteodystrophy in patients undergoing regular dialysis, and it continues to be so despite the increased prevalence of adynamic bone in the contemporary dialysis population. High values for the calcium-phosphorus ion product ($Ca \times P$) in serum are also frequently identified as a risk factor for soft tissue calcification in patients with CKD. Such results largely reflect the frequent and recurrent episodes of hyperphosphatemia that are common in patients undergoing dialysis. They are due less often to episodes of hypercalcemia or to persistently elevated serum calcium concentrations unless treatment has been instituted with large oral doses of calcium or with vitamin D sterols.

Hyperphosphatemia in patients treated with dialysis arises largely from an imbalance between the quantity of phosphorus ingested as an integral and necessary dietary component and the cumulative amount that can be removed during the week with thrice-weekly HD or PD. Because only limited amounts of phosphorus are removed by dialysis, most patients with little or no residual kidney function will be in positive weekly phosphorus balance and experience ongoing phosphorus retention despite the use of phosphate-binding medications. Remarkable improvements in the control of serum phosphorus levels are seen when patients are treated with nightly HD or short-duration HD 6 days per week. The results highlight the limitations of current dialysis strategies for managing phosphorus retention in patients with advanced CKD (35).

For patients treated with conventional dialysis regimens, episodes of hyperphosphatemia may occur more often in those with advanced SHPT. Here, high rates of phosphorus efflux from bone associated with persistently elevated PTH levels lead to the ongoing redistribution of phosphorus into the extracellular fluid, providing an additional source of phosphorus separate from that due to intestinal absorption.

Apart from phosphorus retention and hyperphosphatemia, several recent reports implicate disturbances in calcium metabolism as an important contributor to soft tissue calcification, particularly vascular calcification, in patients with CKD (36,37). The use of supraphysiologic doses of calcium as a phosphate-binding medication and, in one report, more frequent episodes of hypercalcemia have each been associated with arterial calcification in patients undergoing regular dialysis (36,37).

The mechanisms that account for vascular calcification under these circumstances have yet to be clarified. The retention of excess amounts of phosphorus and/or calcium, either alone or in conjunction with recurrent

episodes of hyperphosphatemia and/or hypercalcemia, may facilitate the deposition of mineral in various soft tissues, including blood vessels, in patients with stage 5 CKD. Indeed, plasma is normally supersaturated with respect to calcium and phosphorus, and certain plasma constituents, such as citrate, act as physiologic inhibitors of crystal formation. Vitamin D therapy may aggravate soft tissue calcification either indirectly by raising serum calcium and phosphorus levels or directly by promoting mineral deposition via tissue-specific pathways (38).

Soft tissue calcification can occur in a variety of tissues in patients with advanced SHPT. Affected areas include the skin and subcutaneous tissue, cornea and conjunctiva, muscle, lung, gastrointestinal tract, and cardiovascular system (39–43). Calcification of the heart can involve the myocardium, the electrical conduction system, and cardiac valves. All have potentially serious clinical consequences and may contribute to adverse cardiovascular outcomes.

Although disturbances in calcium and phosphorus metabolism may contribute to the development of soft tissue calcification in patients with CKD (42), a unique role for excess PTH secretion in the pathogenesis of soft tissue calcification is less certain. Patients with adynamic bone disease, in whom PTH levels are either relatively normal or low, also develop extensive soft tissue and vascular calcification (44).

Until recently, passive mechanisms mediated by physical-chemical factors were thought to be the major determinant of soft tissue calcification in renal failure. There is now considerable evidence that vascular calcification is a regulated, cell-mediated process (45,46). A variety of proteins that are normally involved in bone and mineral metabolism have been found to be expressed in calcified vascular lesions. Such findings were reported originally in calcified atheromatous plaques, lesions that occur along the endothelium of arteries as an integral component of atherosclerosis. Subsequent work has demonstrated, however, that many of the same proteins are expressed in arteries affected by medial wall calcification, the type of vascular calcification that is common in patients with CKD (47,48). Thus the localized expression of certain genes and proteins may play a pivotal role in the uptake and/or deposition of minerals in arterial tissues.

Despite these findings, it remains uncertain whether gene expression and protein synthesis are initiating events in the process of vascular calcification, or whether various bone-related proteins are expressed in arterial tissue only after mineral deposition has begun through unregulated or dystrophic mechanisms. In this regard, the noncollagenous bone protein osteopontin has been found using immunohistochemical methods in noncalcified specimens of iliac artery obtained at the time of renal transplantation in patients with CKD (49). Such findings are consistent with the view that the localized expression of this particular bone-related protein precedes the development of overt vascular calcification in selected conditions.

Other genes and proteins act as physiologic inhibitors of calcification in various soft tissues. Key among these is matrix Gla-protein (MGP), which plays a critical role in preventing the calcification of arteries and epiphyseal growth plate cartilage during development. Mice with inactivating mutations of the gene for MGP have extensive arterial calcification and die within a few months of birth from hemorrhage due to arterial rupture, findings that emphasize the importance of MGP as an inhibitor of inappropriate arterial calcification (50). Whether the synthesis and metabolism of MGP are affected by reductions in kidney function or by alterations in mineral metabolism that arise due to advanced renal failure is not currently known. Nonetheless, warfarin interferes with the gamma-carboxylation of MGP, and the clinical use of this therapeutic agent in patients with ESRD has been identified in several reports as a risk factor for CUA (51,52).

Calcific uremic arteriolopathy is a life-threatening complication of CKD that is characterized by extensive calcification in medium and small arteries, particularly those located in subcutaneous tissues (11). Proliferation and necrosis of cells along the intimal layer of arteries lead to occlusion of the vessel lumen, tissue ischemia, skin ulceration, and gangrene. As reported initially, the arteries of the distal extremities were affected most severely, and ischemia of the digits of the hands and feet was a prominent finding (53). Serum PTH levels were often, but not always, elevated. Several reports described dramatic improvement after parathyroidectomy, suggesting that very high serum PTH levels played a key pathogenic role (54,55).

More recently, a proximal form of CUA has become more common (56). The syndrome is characterized by extensive ulceration of the skin over the upper thighs, buttocks, and abdominal wall. Apart from elevated serum phosphorus and $Ca \times P$ levels, female gender and obesity are important risk factors for the proximal form of CUA (51). The overall mortality rate for patients with CUA has been recently reported to be 39% within 6 months of diagnosis (57), with mortality exceeding 80% in those who developed skin ulceration (57).

The incidence of CUA has increased in recent years and now occurs in 4.5% of patients treated with either PD or HD (57). By comparison, the prevalence of CUA in 1993 was estimated to be only 1% (58). The widespread use of calcium-containing compounds as phosphate-binding agents and large doses of vitamin D sterols to treat SHPT have each been implicated as contributors to the increased incidence of CUA. In a recent case-control study, patients given calcium salts and vitamin D had a higher risk of CUA than those not receiving these therapeutic agents (57). As mentioned previously, treatment with the anticoagulant warfarin has been identified repeatedly as a risk factor for CUA. Such findings suggest that this life-threatening disorder may, to some extent, be preventable (52,57).

Cardiovascular Complications

The etiology of cardiovascular disease in patients with CKD is complex and not fully understood. Numerous cardiovascular risk factors are present in patients with CKD, including hypertension and extracellular fluid volume overload, diabetes and glucose intolerance, dyslipidemia, and alterations in homocysteine metabolism.

Even when combined with other established cardiovascular risks, such as age, gender, obesity, and tobacco use, the risk of death from cardiovascular causes in patients undergoing dialysis far exceeds that predicted by traditional assessments (59). It is likely therefore that previously unappreciated risk factors contribute substantially to adverse cardiovascular outcomes in such patients.

Recent reports have implicated various disturbances in mineral metabolism as potential contributors to the development of cardiovascular disease in patients undergoing long-term dialysis (36,37). Several of them, such as elevated PTH levels, hyperphosphatemia, and high values for serum Ca × P, are integral components of SHPT. Others are more closely related to the clinical management of the disorder. These include the therapeutic use of large doses of vitamin D sterols and calcium-containing phosphate-binding agents.

Parathyroid hormone itself has been reported to have a variety of adverse cardiovascular effects. Studies in rats indicate that PTH increases myocardial calcium content and adversely affects energy utilization in myocardial tissue (60). A recent assessment based on data from the U.S. Renal Data System (USRDS) registry suggested that PTH concentrations greater than 495 pg/ml were associated with a higher risk of sudden death from cardiovascular disease compared to patients with values in the range of 91–197 pg/ml (61). It should be noted, however, that very low plasma PTH levels have also been associated with excess mortality in patients with stage 5 CKD (62).

For dialysis patients, elevated serum calcium levels have been linked to myocardial dysfunction, and there are inverse relationships between left ventricular ejection fraction and both myocardial calcium content and plasma PTH concentrations (43). As noted previously, elevated PTH, phosphorus, and Ca × P levels have each been associated with cardiac causes of death (61). Patients whose serum phosphorus level exceeded 6.5 mg/dl had a higher risk of death from coronary artery disease and from sudden cardiac death than those with normal serum phosphorus concentrations (2.4–4.1 mg/dl) (61). Although alterations in mineral metabolism are now thought to contribute substantially to cardiovascular disease in patients with CKD (63), the interactions among and the precise relationships between these abnormalities and more traditional cardiovascular risk factors remain uncertain (64).

The frequency and extent of arterial and cardiac calcification in patients with CKD have become widely appreciated only recently. Calcification of the aortic valve and/or mitral valve occurs in more than half of adult patients treated with regular HD, a prevalence that is far greater than that in the general population. Valve dysfunction due to extensive calcification may lead to congestive heart failure (65). Increasing age and longer duration of treatment with maintenance dialysis have each been associated with echocardiographic evidence of cardiac valve calcification in patients with stage 5 CKD (66), and high values of serum Ca × P also appear to contribute (67).

Whereas increasing age is a major determinant of coronary artery calcification both in the general population and in those undergoing dialysis, duration of dialysis is probably a more important risk factor for coronary artery calcification in younger individuals receiving dialysis (36). Studies using the noninvasive technique of electron beam computed tomography (EBCT) also suggest that elevated Ca × P values also contribute (36). Even modest elevations in Ca × P of approximately 55 mg^2/dl^2 appear to increase the risk of myocardial calcification (68). Cardiac calcification may lead to myocardial fibrosis with left ventricular dysfunction, and calcifications that involve the electrical conduction system of the heart can cause conduction defects and cardiac arrhythmia.

Although coronary artery calcification is common in adults with ESRD, high coronary artery calcification scores as measured by EBCT cannot be taken as evidence of overt atherosclerotic coronary artery disease in this patient population. Calcification in the tunica media of arteries is a hallmark of patients with CKD, but imaging methods such as EBCT are unable to distinguish between calcium deposits along the intimal layer of arteries that are associated with atherosclerotic plaques and those located in the tunica media due to medial wall calcification. The hemodynamic consequences of these two distinct types of arterial calcification are quite different. Stenoses of the arterial lumen, reductions in blood flow with tissue ischemia, and arterial thromboses and occlusion are major concerns with atherosclerotic vascular lesions. In contrast, systolic hypertension, widening of the pulse pressure, and increases in pulse wave velocity caused by diminished arterial compliance are major consequences of medial wall calcification (69). Both types of arterial disease probably contribute to the very high rates of death from cardiovascular causes in patients with ESRD, but the relative importance of each remains uncertain.

Metabolic Disturbances

Abnormal lipid metabolism, insulin resistance, and glucose intolerance represent distinct risk factors for cardiovascular disease in patients with CKD. Some studies suggest that SHPT contributes materially to these disturbances. Although the serum levels of low-density lipoprotein (LDL) cholesterol are elevated infrequently in patients treated with HD, high-density lipoprotein (HDL) cholesterol concentrations are often reduced. Moreover, serum triglyceride levels are commonly elevated. Some studies suggest that selected lipoprotein fractions, such as apolipoprotein E, convey a disproportionate cardiovascular risk for those undergoing long-term dialysis. Unfortunately little is known about the potential benefits of lipid-lowering therapy in patients with CKD.

Alterations in calcium metabolism and high PTH levels have each been implicated as factors that can adversely affect lipid metabolism and glucose utilization in patients with CKD. Both disturbances raise intracellular or cytosolic calcium concentrations, changes that have been linked to abnormal lipid metabolism and to impairments in glucose utilization and insulin secretion (70,71). Insulin sensitivity in healthy subjects has been inversely related to plasma PTH concentrations (72). It is possible therefore that SHPT contributes substantially to certain abnormalities in intermediary metabolism in patients with CKD.

Other Complications of Uncontrolled SHPT

Pruritus is common in patients with SHPT. It can be severe and disabling. Persistently elevated serum phosphorus levels are a major contributor to this problematic manifestation of advanced CKD, but high PTH levels are likely to play an independent role. Pruritus improves substantially or resolves completely in many patients after parathyroidectomy (73,74).

Anemia is common both in patients with moderate to advanced CKD and those treated with dialysis. It has been identified consistently as an independent risk factor for left ventricular hypertrophy and for hospital admissions due to cardiac and noncardiac causes (75). As noted previously, SHPT can cause marrow fibrosis and aggravate the anemia of CKD. The extent of marrow fibrosis is an important determinant of the therapeutic response to treatment with recombinant human erythropoietin (12). High PTH levels may also increase the fragility of erythrocytes, thereby shortening red blood cell survival, and directly inhibit erythropoiesis (76–78).

Current Management Strategies and Future Prospects

The safe and effective management of SHPT remains a challenge for clinicians. Successful treatment lowers PTH levels and improves metabolic bone disease with symptomatic benefit for many patients. Nevertheless, disturbances in calcium and phosphorus metabolism, either alone or together with the interventions designed to manage SHPT, can have serious adverse consequences. Dietary phosphorus restriction confounds the nutritional management of patients with CKD. It can preclude the achievement of adequate protein nutrition and often results in suboptimal dietary calcium intake. In contrast, the use of large oral doses of calcium-containing salts such as calcium carbonate and calcium acetate as phosphate-binding medications can lead to episodes of hypercalcemia, render total body calcium balance quite positive, and aggravate soft tissue and vascular calcification (79). Vitamin D sterols such as calcitriol, and more recently introduced vitamin D sterols such as paricalcitol and doxercalciferol, effectively lower PTH levels in dialysis patients with SHPT. These therapeutic agents promote intestinal calcium and phosphorus absorption to varying degrees, however, and increases in serum calcium and/or phosphorus levels during treatment often limit the doses that can be given safely in an effort to lower PTH levels (80–82). Caution is thus required to avoid episodes of hypercalcemia and hyperphosphatemia with the attendant risk of soft tissue and vascular calcification (61). For these reasons, the benefits and liabilities of treating SHPT using currently available strategies should be assessed carefully before therapeutic interventions are initiated.

Recent advances in vitamin D pharmacology are encouraging, and vitamin D analogues with a greater therapeutic index are now available for clinical use. Together with the availability of calcium-free phosphate-binding agents, new vitamin D sterols offer a potentially wider margin of safety when managing mineral metabolism in patients with CKD (83–85). Such developments may ultimately improve the overall management of patients with SHPT. SHPT remains inadequately controlled, however, in many patients, and the disease often progresses despite treatment.

The identification and cloning of the calcium-sensing receptor (CaR) has contributed greatly to our understanding of the physiology of calcium and phosphorus metabolism and the mechanisms that regulate PTH secretion (86,87). The CaR represents the molecular mechanism by which parathyroid cells recognize changes in blood ionized calcium concentration and modify PTH secretion accordingly. Because the CaR is the most proximate determinant of PTH secretion not only in individuals with normal renal and parathyroid gland function but also in patients with CKD (88,89), agents that interact with the CaR offer a way of altering PTH secretion in a therapeutic context (90).

Calcimimetic agents are small organic molecules that act as allosteric activators of the CaR (91,92). In parathyroid tissue, they lower the threshold for CaR activation by extracellular calcium ions and thus diminish PTH release. Their mechanism of action differs fundamentally from that of the vitamin D sterols, which act primarily to suppress prepro-PTH gene transcription. As such, calcimimetic compounds offer a novel approach to managing excess PTH secretion in patients with CKD (90).

The oral administration of calcimimetic agents invariably produces substantial reductions in plasma PTH levels within only a few hours in patients with mild, moderate, or severe SHPT (93,94). Patients who fail to respond in this manner have yet to be identified. In clinical trials among patients with SHPT due to stage 5 CKD, sustained reductions in PTH levels have been achieved for periods of as long as 2 years. Moreover, decreases in serum phosphorus levels and in values for the $Ca \times P$ ion product have been reported during calcimimetic therapy in several studies (93,97), biochemical changes that may reduce the risk of soft tissue and vascular calcification.

The mechanisms that account for decreases in serum phosphorus levels during treatment with calcimimetics have yet to be clarified, but the situation may be similar to that seen after surgical parathyroidectomy, a condition known as the "hungry bone syndrome." Because calcimimetic compounds abruptly diminish PTH secretion without increasing intestinal phosphorus or calcium absorption, rapid decreases in PTH levels may reduce phosphorus efflux from bone and lower serum phosphorus concentrations (93,95,96). This biochemical change differs substantially from that seen during treatment with vitamin D sterols, which often raise serum phosphorus levels.

Because of their novel mechanism of action, calcimimetic compounds can be used in combination with other agents such as vitamin D analogues to lower plasma PTH levels in patients with SHPT. Such an approach may be particularly effective for those with advanced disease (93,94,96,97).

Apart from diminishing PTH secretion, calcimimetic compounds may retard the development of parathyroid gland hyperplasia and increase bone mass (98–100). If confirmed by additional clinical assessments, these ancil-

lary features of calcimimetic therapy would broaden their appeal as an approach for managing SHPT in patients with CKD.

Conclusion

Inadequately controlled SHPT causes metabolic bone disease and may aggravate soft tissue and vascular calcification in patients undergoing long-term dialysis. The management of SHPT with vitamin D sterols and calcium-containing phosphate-binding agents also involves considerable risk, including adverse effects on calcium and phosphorus metabolism, arterial calcification, and the development of cardiovascular disease. As such, therapeutic guidelines are evolving and new treatment strategies are being developed.

Calcimimetic compounds are a potentially important new class of therapeutic agents that control excess PTH secretion without raising serum calcium or phosphorus levels. When used either alone or together with vitamin D sterols, calcimimetic agents effectively lower plasma PTH levels while favorably affecting several biochemical disturbances that have been associated with adverse clinical outcomes. Calcimimetic compounds thus have considerable promise as a new therapeutic intervention for SHPT in patients with CKD.

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