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Overview of renal bone disease: Causes of treatment failure, clinical observations, the changing pattern of bone lesions, and future therapeutic approach

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Divalent ions, metabolism abnormalities, and hyperparathyroid bone disease noted in patients with chronic kidney disease (CKD) develop early in the course of renal insufficiency. In the last two decades, therapy has focused mostly in treating the bone lesion as well as controlling the secondary hyperparathyroidism. However, recent large epidemiologic studies have highlighted the importance of both hyperphosphatemia and an increase in the calcium burden as major factors leading to the high mortality rate of end-stage renal disease (ESRD) patients [1–3]. Furthermore, a recent study strongly suggests the high mortality rate may be due to an increase in cardiac events [4]. In the present manuscript, the causes for the failure of the original therapeutic goals will be discussed first; the changing pattern in the bone lesions will be assessed second; and third, future therapeutic approaches will be explored, with special emphasis in early therapy and avoiding the cardiovascular abnormalities recently noted in CKD patients.

FAILURE IN ACHIEVING THERAPEUTIC GOALS

In a recent article, Parfitt [5] has suggested that the nephrologist has focused more in inhibiting parathyroid hormone (PTH) secretion rather than preventing the growth of parathyroid gland hyperplasia. In general, most nephrologists have commenced vitamin D therapy in renal patients at a late stage, when the level of PTH was higher than 3 to 4 times normal levels. In addition, control of hyperphosphatemia and hypocalcemia, though a desirable goal, was not considered as important. Until recently, the available therapeutic agents to achieve the above mentioned goals were calcitriol (or its analogs) and calcium-containing phosphorus binders. However, abnormalities in the biological markers of secondary hyperparathyroidism develop late in the course of CKD; by this time significant nodular parathyroid hyperplasia is already present [6]. Thus, it is not surprising that late therapy often fails and, in addition, an increased burden of Ca and P (together with a high Ca $\times$ P product) may already be present. Also, late commencement of therapy means higher doses of calcitriol therapy [7].

CONSEQUENCES OF THE THERAPEUTIC FAILURE

The most immediate consequence and/or side effect of current therapy for secondary hyperparathyroidism is the increase in soft tissue calcification: That is visceral, periarticular, and, most importantly, cardiovascular. As it was mentioned earlier there is a high mortality rate in ESRD patients. A significant positive Ca and P balance is a significant factor in the morbidity and mortality of ESRD patients [1]. Thus, patients with serum P concentrations $>$6.5 mg/dL and a Ca $\times$ P product $>$72 mg/dL have a higher mortality rate (27% and 34%, respectively) than patients with serum P $<$6.5 mg/dL and a Ca $\times$ P product $<$52 mg/dL. Recently, Ganesh et al [4], in a large dialysis population ($>$12,000 ESRD patients), have shown that patients with plasma P $>$6.5 mg/dL have a 56% higher mortality risk mostly due to coronary artery disease; and a 27% increase risk of sudden death. Furthermore, for each 10 mg/dL increment in the Ca $\times$ P product, there was an 11% increment in sudden death. Chertow et al [3] has recently evaluated data of 40,000 dialysis patients. The plasma Ca and P of these patients were analyzed as an independent risk at intervals of 0.5 and 1 mg/dL, respectively. The relative risk was noted to be the lowest at plasma P concentration between 3 and 5 mg/dL; then there was a progressive increment in the risk, which was parallel with the increment in plasma

Key words: chronic kidney disease, osteodystrophy, parathyroid hormone.

P concentration. The mortality rate for Ca, taking as reference concentration of 9 to 9.5 mg/dL, was 0.80 for plasma Ca <8 mg/dL and 1.47 for a Ca >11 mg/dL.

CLINICAL SIGNS AND SYMPTOMS OF OSTEODYSTROPHY

First of all, it is necessary to bear in mind that bone disease in patients with chronic renal failure (CRF) is usually asymptomatic. Thus, symptoms appear late in the course of renal osteodystrophy. By the time symptoms are present, the patient usually has significant biochemical abnormalities and histologic evidence of bone disease. The usual symptoms of bone pain, muscular weakness, periarthritis, and pruritus are usually absent. However, two clinical syndromes have been increasing in frequency and deserve some discussion. They are coronary artery calcifications and calciphylaxis.

Recent evidence has shown a high prevalence of coronary artery calcifications in the ESRD population, and they probably play a major role in the high cardiac morbidity and mortality rates. Indeed, strong relationships have been found between cardiac deaths and factors that favor metastatic calcifications (i.e., hyperphosphatemia and increased Ca × PO4 product) [8]. In a large national study of data from more than 12,000 ESRD patients, higher mortality rates from coronary artery disease were found in patients with hyperphosphatemia (serum P >6.5 mg/dL) compared to patients with serum P <6.5 mg/dL (relative risk 1.41; $P < 0.0005$). The risk for sudden death was also increased in patients with hyperphosphatemia as well as in patients with elevated Ca × PO4 products (relative risk 1.07 per 10 mg^2/dL^2) and those with PTH levels greater than 495 pg/mL [4]. Calcifications of cardiac tissue have been reported in nearly 60% of dialysis patients [9-10]. These are most significant in the coronary arteries.

Coronary artery calcifications are much more common and more severe in patients on hemodialysis than in subjects without renal failure [9-10]. New non-invasive techniques that utilize the electron-beam computed tomography (EBCT) to detect coronary artery calcifications have illuminated this issue [11–12]. EBCT has high spatial and temporal resolution, and ultrafast (at subsecond intervals) imaging is triggered by the patient's EKG rhythm, which makes it well suited for cardiac imaging. Calcification of atherosclerotic plaques is found in the advanced stages of plaque transformation [11]. The extent of calcification noted by this technique correlates well with the severity of atherosclerotic lesions detected by coronary angiography [12]. When compared to coronary angiography as the reference standard, EBCT detected coronary artery disease with a sensitivity of 93% and a specificity of 73% [12]. Coronary artery calcifications detected by EBCT were found in the majority of patients on dialysis [9-10]. Braun et al [10] found that the incidence of coronary artery calcifications was 2.5-fold to five times greater in 49 patients on dialysis compared to 102 no dialysis patients of similar age.

Furthermore, these calcifications worsened in the dialysis patients when EBCT studies were repeated one year later. Goodman et al [13] observed coronary artery calcifications to be highly prevalent (14 of 16 patients) in young adults, aged 20 to 30 years on dialysis, compared to healthy subjects of the same age (3 of 60 subjects). Aside from coronary artery calcifications, calcium deposits of the valves, especially the mitral and aortic valves, and of the myocardium are very common. Soft tissue calcifications may be contributing to conduction abnormalities and arrhythmias, left ventricular dysfunction, aortic and mitral stenosis, ischemia, congestive heart failure, and death. Most studies have found correlations of calcifications with uncontrolled hyperphosphatemia, an increased Ca × PO4 product, and years on dialysis [2–3, 6]. Patients with greater intake of oral calcium had a higher incidence of coronary artery calcifications [13].

These data suggest that long-term imbalances in calcium (Ca) and phosphorus (P) are factors in the development of cardiac calcifications. They also raise the concern that long-term treatment with high doses of calcium-based phosphate binders along with inappropriate vitamin D therapy may contribute to these calcifications. Vigilant monitoring of serum Ca and P, and Ca × P product may reduce the incidence of cardiac calcification and its related morbidity and mortality. Control of serum Ca and P, and avoidance of excessive Ca intake should be viewed as part of a comprehensive approach to modify risk factors for coronary artery disease, which are so prevalent in the ESRD population [9].

Another serious problem of soft tissue calcification is calcific uremic arteriolopathy (CUA), also known as calciphylaxis. These are necrotic skin lesions that usually present as painful violaceous mottling similar to livedo reticularis, or as painful nodules or panniculitis. Seyle [14] first described a syndrome in the experimental animal in 1962 and postulated that two steps are required to produce ectopic systemic calcifications. First, a systemic sensitization induced by agents such as parathyroid hormone (PTH), vitamin D, or a diet high in calcium (Ca) and phosphorus (P). Second, after a time interval (the "critical period"), exposure to appropriate challenging agents by subcutaneous injections resulted in macroscopic visible deposits of calcium salts (hydroxyapatite) systematically and at the site of injection within two to three days. The challenging agents included local trauma, iron salt, egg albumin, polymyxin, and glucocorticoids. Selye named the syndrome "calciphylaxis." A few years later, a syndrome characterized by peripheral ischemic tissular necrosis, vascular calcifications, and cutaneous ulcerations was reported in uremic patients [15]. Because

of its resemblance to Selye's animal model, it was named "calciphylaxis [15]." However, the syndrome described in the uremic patient only resembles Selye's model. Though a useful concept earlier, the analogy with Selye's model may not be warranted because the term "calciphylaxis" has pathogenic implications that have not been confirmed in humans. Thus, significant differences exist between Selye's model and uremic calciphylaxis. The former was characterized by metastatic systemic calcifications developing after significant invasive manipulations of the animal model, but vascular calcifications were not present. The latter occurs primarily in the presence of uremia with abnormalities in divalent ions (i.e., PTH, hypercalcemia, and hyperphosphatemia) and most importantly, vascular calcifications were noted at the lesions. Retrospectively, it appears that uremic soft tissue calcification (tumoral calcinosis) is the syndrome most analogous to Selye's. It should be emphasized that Selye's model did not exhibit the histology consistently described with uremic calciphylaxis (i.e., small-vessel calcifications and intimal hypertrophy in association with panniculitis and small-vessel thrombosis) [15].

However, clinically it is important to review certain pathogenic factors. First, the presence of a uremic milieu together with a high Ca × P product was noted in the majority of reports [15–18]. Diffuse vascular calcifications were frequently noted in the early days of maintenance dialysis [19]. CUA was noted in 20% of dialysis patients with secondary hyperparathyroidism [19]; it increased to 58% in patients with clinical evidence of hyperparathyroidism and to 75% in patients with severe overt hyperparathyroidism [20]. Still, even in these early days at a time when secondary hyperparathyroidism was common, calciphylaxis was uncommon.

Second, the Ca content of the skin was also an important pathogenic factor because it was noted to be high in dialysis patients developing CUA. [21] It also appeared to occur when a very high dialysate Ca concentration of 4.0 mEq/L was used [22]. In addition, a decrease in dialysate Ca dramatically improved CUA in some patients whereas a high dialysate Ca concentration aggravated soft tissue calcification [22]. Furthermore, CUA was associated with hypercalcemia induced by large oral doses of calcium carbonate, and it was reversed by discontinuing Ca carbonate [23]. It is worth emphasizing that the use of Ca-containing binders is common, and that many dialysis patients still ingest large doses of elemental Ca. The long-term effect of this large Ca load on the dialysis population remains to be established. It is striking that almost all patients developing CUA described in recent years were ingesting Ca-containing binders.

A third important pathogenic factor was the presence of high PTH levels. Earlier, it appeared that hyperparathyroidism was an important risk factor in the development of CUA. [22] Gipstein et al [17] reported a series of patients with CUA, most with peripheral digital ulcers in which parathyroidectomy (PTX) resulted in dramatic healing of the ulcers and total disappearance of the syndrome in 61 percent of the patients. A period of marked hyperphosphatemia was present in each patient at some time prior to the appearance of CUA. Later, hyperphosphatemia was also associated with CUA [19, 24]. In these patients who had relatively low PTH levels, severe phosphorus restriction was shown to reverse CUA [18, 24].

More recently, this syndrome has been noted in patients with PTH levels close to normal and/or with minimal divalent ion abnormalities, which highlights the evolving nature of CUA. We recently reported 14 patients with CUA in whom only 4 (28%) had elevated PTH levels (870 ± 234 pg/mL) [25]. In the remaining 10 patients, Ca, P, and PTH (<250 pg/mL) all appeared to be well controlled. With the advent of calcitriol (CTR) and better control of hyperparathyroidism, other factors have surfaced and become more relevant in the triggering of CUA. As reported by Coates et al [16] and Bleyer et al [18], the presence of obesity, especially in white women, is an important predisposing factor to developing CUA. Morbid obesity was present in 11 of our 14 patients (79%) with CUA [16]. Supposedly, the areas rich in adipose tissue may be more prone to small-vessel damage, which may promote calcifications before cutaneous lesions and necrosis of the skin become clinically apparent. Coates et al [16] noticed a significant weight loss preceding the development of the skin lesion in 7 of 16 patients. Furthermore, Bleyer et al [18] in a logistic regression analysis identified obesity and low serum albumin as highly predictive of CUA. Others have noted an association with insulin-dependent diabetes mellitus and CUA; however, no mention was made of obesity. Interestingly, in four patients the lesions developed in areas that had obviously serve as sites of insulin injection [18]. Local trauma, such as subcutaneous injections of heparin or iron dextran, may also be precipitating factors in the local development of CUA [18].

The relative risk of CUA increased with weight increase. This is important because severe morbid obesity is uncommon in dialysis patients and these patients may be easily identified. The impression is that patients with proximal calciphylaxis have poorer prognoses than those with acral CUA. Thus, Hafner et al [26] evaluated the role of PTX in 38 of 58 patients who survived compared with 13 of 37 patients who did not undergo PTX. Most importantly, 40 of the 53 patients (75%) with distal location of necrosis survived compared with 11 of 42 patients (26%) with proximal CUA ($P = 0.00001$).

In summary, CUA is a relatively rare but life-threatening complication in uremic patients. The overall clinical picture of this syndrome has gradually changed as our therapeutic approach (discussed later) has changed.

THE CHANGING PATTERNS OF RENAL BONE DISEASE

As mentioned above, the therapeutic practice of the last decade has resulted in a change in the spectrum of bone disease in the ESRD population. The two common bone lesions still noted in renal patients include:

High bone turnover disease

This bone lesion is the result of the prevailing high PTH levels noted in patients with CKD. This lesion still is present in more than 50% of CKD patients. The persistence of this lesion is due to several factors. Most important is the very late commencement of vitamin D therapy, at a time when parathyroid gland hyperplasia is already significant. Second, dosing of vitamin D therapy needs to be appropriate and commensurate with the PTH levels. Both overtreatment and undertreatment with vitamin D is not uncommon. Third, the high incidence of hypercalcemia and hyperphosphatemia as the result of the late therapeutic approach with vitamin D has resulted in cessation of therapy, leading to a substantial number of patients not being treated for a significant secondary hyperparathyroidism. These patients eventually end up having surgical intervention (parathyroidectomy), which in turn will invariably lead to a low bone turnover lesion [i.e., adynamic bone disease (ABD)].

Low bone turnover disease

This bone lesion is usually associated with low PTH level. In the past this lesion was noted in ESRD patients developing aluminum toxicity. Today, despite a decrease in the use of aluminum-containing P binders, this bone lesion, ABD, has been described with increasing frequency. The pathophysiology of low bone turnover states is not well known. This bone lesion is characterized by low bone volume and it has been steadily increasing in CKD patients. The most factors associated with the low PTH levels are the presence of diabetes, advanced age, and, most importantly, overtreatment with both Ca-containing phosphorus binders and vitamin D.

FUTURE GOALS IN THE THERAPY OF RENAL BONE DISEASE

Strategies for the future must include (*1*) prevention of parathyroid hyperplasia, and (*2*) avoidance of a positive balance of Ca and phosphorus (P). Therapy should be aimed at the early stages of CKD. The data over the development of parathyroid gland hyperplasia in CKD patients shows that secondary hyperparathyroidism occurs at early stages of CRF. Martinez at al [27, 28] noted in 150 patients with various degree of renal insufficiency an increase in PTH as creatinine clearance decreased to

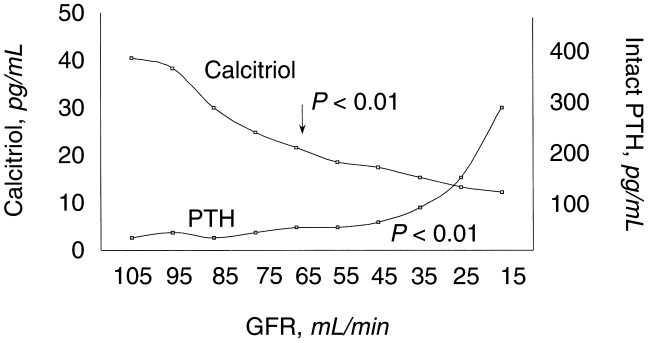

Fig. 1. A significant decrease in calcitriol suggests that this may be a factor in the cause of secondary hyperparathyroidism.

<60 to 70 mL/min. As can be noted in Figure 1, a significant decrease in calcitriol is noted at an earlier stage, suggesting that the deficit in calcitriol may be a factor in the cause of secondary hyperparathyroidism. Thus, this may be the time when therapeutic intervention may be advisable. However, it is not clear whether the administration of calcitriol (to correct its deficit) to patients with CRF may be indicated. The maintenance of physiologic levels of calcitriol in patients with renal insufficiency may not be advisable, since vitamin D therapy in these patients may result in an increase in the Ca and P burden. In normal subjects, calcitriol replacement leads to a marked increased urinary excretion of Ca and P, and the noted mild deficit of calcitriol in early CRF may be an adaptive response to protect the kidney from further renal function deterioration [29]. In this situation, the administration of vitamin D, by causing a significant increase in intestinal Ca and P absorption, may be harmful. In patients with creatinine clearances of 50 mL/min, P restriction results in a decrease in PTH and normalization of plasma calcitriol [30–32]. Unfortunately, this approach is not practical. In addition, the long-term effects of protein restriction, caused by the phosphate restriction, are not known. A new alternative is the use of a new vitamin D analog that has minimal effects on gut absorption of Ca and P. This analog is paricalcitol. Data is not yet available on the use of paricalcitol in CKD patients stages 3 and 4. At present, a prospective, double-blind randomized multicenter study is being conducted using oral paricalcitol in these patients. The results may be available next year. Another alternative in CKD, stage 3 and 4, is the use of P binders. Despite the fact that most of patients with CKD, stage 3, have normal serum P, the use of the binders may mimic the results of dietary P restriction, leading to stimulation of calcitriol synthesis and suppression of PTH secretion. Unfortunately, at present, studies on the use of safe P binders to be used in CKD are not available. Furthermore, none of the available P binders may be safe for therapy in CKD patients stages 3 and 4. Thus, the use of Ca-containing P

binders may lead to Ca overload and toxicity, and the use of a non-Ca binder such as sevelamer promotes an increment in the protonated amines that may result in hyperchloremic acidosis.

In ESRD patients, P restriction may directly inhibit PTH synthesis, but it does not induce any changes in the levels of calcitriol; by this time, parathyroid gland hyperplasia is established. At this stage the use of vitamin D usually induce a positive Ca and P balance with a high incidence of hypercalcemia and hyperphosphatemia. The new vitamin D analogs, which inhibit PTH but minimize the hypercalcemic and hyperphosphatemic effects, may be be indicated.

Rationale for new vitamin D analogs

Substantial evidence has accumulated over the last number of years showing that it is possible to obtain some selectivity of the effects of vitamins by the utilization of vitamin D analogs [33, 34]. The strategy has been to design a calcitriol analog for its ability to decrease PTH secretion, and at the same time, to have lesser effects on the ability to elevate serum Ca and P. The result would be to correct secondary hyperparathyroidism while minimizing the toxicity that results from elevations on serum Ca and P.

A wide variety of vitamin D analogs were screened for this purpose and include 22-oxa-calcitriol and an analog-based on the vitamin D_2 structure, 19-nor-1,25-dihydroxy-vitamin D_2 (paricalcitol) [35–37]. Later, 1-α-hydroxy-vitamin D_2 (doxercalciferol) was evaluated for this purpose. This sterol undergoes 25-hydroxylation in the liver to form the active metabolite, 1,25-dihydroxyvitamin D_2. It may also enter other metabolic pathways [38]. The use of the vitamin D_2 structure as the basis for the analogs stems from observations many years ago that vitamin D_2 compounds may be less toxic in animals [39]. The use of vitamin D analogs has also been successfully applied to many other fields of study. While 1-α-hydroxyvitamin D_3 is widely used outside the United States, the two compounds in use in this country include 19-nor-1,25-dihydroxyvitamin D_2 and 1-α-hydroxyvitamin D_2.

Effects of 19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol)

As a result of screening a large number of vitamin D compounds, paricalcitol was noted to be a potent suppressor of PTH secretion in vitro, and accordingly was evaluated extensively in animal models in vivo, where it was found to be an effective suppressor of PTH secretion in both normal and uremic animals, and at the same time, to have a considerably lesser ability to increase serum calcium or phosphorus than calcitriol [33–35] in experimental animals in vivo. Thus, while paricalcitol had one third the potency of calcitriol in decreasing PTH secretion, it had only one tenth the potency of calcitriol in terms of its ability to raise serum Ca or P. Taken together, paricalcitol has a three-fold increase in selectivity for suppression of PTH compared to the natural hormone calcitriol. On the basis of these experimental studies, clinical trials of paricalcitol in ESRD patients were conducted; they were double blind, randomized, and multicenter. Paricalcitol was shown to effectively suppress PTH secretion without the toxic side effects of elevated Ca and/or P [40, 41]. During these studies, as well as in studies in experimental animals, it was apparent that paricalcitol was not totally devoid of a hypercalcemic effect, and overtreatment may result in hypercalcemia [41, 42]. The few episodes of hypercalcemia occurred when intact PTH values were suppressed to near 100 pg/mL, levels that are considered to be undesirably low. The long-term effects of paricalcitol have also shown the absence of hypercalcemia in longer-term studies in ESRD patients [23–42]. Therefore, it is important to emphasize that vitamin D analogs, like paricalcitol, should not be considered non-calcemic vitamin D analogs, but rather, be considered to have less calcemic activity than the native hormone. Studies by Lerma et al [43] have evaluated the relative effects of these compounds on hyperphosphatemia in patients and found, during a comparative trial, that paricalcitol was associated with fewer episodes of hyperphosphatemia at all phases of the study than calcitriol. Recently, a double-blind randomized multicenter study comparing the safety and effectiveness of intravenous paricalcitol and calcitriol in suppressing PTH concentration in hemodialysis patients has been reported [44]. A total of 263 randomized patients from national and international sites were enrolled. Paricalcitol-treated patients achieved a 50% reduction in PTH values faster than calcitriol treated patients ($P < 0.02$). Most importantly, paricalcitol-treated patients had significantly fewer sustained episodes of hypercalcemia and/or increased Ca $\times$ P product than calcitriol patients ($P = 0.008$). These clinical studies are again consistent with the effects noted in experimental uremic animals. Thus, it appears that from a variety of studies in experimental animals and in patients, paricalcitol is an effective agent for the suppression of secondary hyperparathyroidism in ESRD patients, and because of its lesser ability to raise serum calcium and phosphorus than the parent compound, calcitriol, it provides a wider therapeutic window for the control of hyperparathyroidism in this patient group.

Effects of 1α-dihydroxyvitamin D_2 (doxercalciferol)

This vitamin D analog has been recently introduced in this country for the control of hyperparathyroidism in ESRD patients. As discussed above, interest in the vitamin D_2 compounds arose because of observations by Sjogen et al [39], which indicated that while vitamin D_2 and vitamin D_3 sterols were equally effective in curing

rickets in experimental animals, and had similar effects on calcium transport in the intestine and on phosphate uptake, it appeared that the D_2 compounds were less toxic in small groups of experimental animals receiving very large doses of either 1-α-hydroxyvitamin D_2 or 1-α-hydroxyvitamin D_3. In this study, there was a higher mortality in the group receiving doses of 5 to 20 μg/kg/day of 1-α-hydroxyvitamin D_3 compared with those receiving or 1-α-hydroxyvitamin D_2. The reason for the greater toxicity of the 1-α-hydroxyvitamin D_3 groups was not apparent from these studies, since the increment in serum calcium appeared to be similar with D_2- and D_3-based compounds, as were the effects on intestinal calcium transport [39]. Similar studies subsequently have re-evaluated differences in serum Ca and P between these two compounds in the ovariectomized rat model. The effects of both compounds on the ability to elevate serum Ca and P and to decrease levels in intact PTH were identical [45]. Thus, from the results obtained in experimental animals, the vitamin D_2-based sterol appears to have equal potency compared to the D_3 counterpart, in terms of suppression of PTH, increasing Ca absorption from the intestine, and elevating serum P. Recently, the effects of doxercalciferol and paricalcitol on serum Ca, P, and Ca × P product has been compared in the experimental uremic animal. While doxercalciferol has a significant increment in Ca, P, and Ca × P product (similar to calcitriol), paricalcitol did not [46]. Thus, there appears to be no evidence for selectivity for PTH suppression with this compound at the present time. Doxercalciferol has been administered successfully to ESRD patients with, and initially utilized in an oral form, was found to be effective in decreasing PTH [47]. Subsequently, it was also introduced in intravenous form, and more extensive studies have shown that both oral and intravenous forms were effective in decreasing PTH secretion [48, 49]. However, there tended to be higher serum Ca values with the oral compound than with the intravenous, and serum P values appeared to be higher than with the intravenous compounds. Overall, between 8% to 15% of all determinations for serum Ca were in the hypercalcemic range for intravenous and oral treatments, respectively, and between 14% and 17% samples were associated with hyperphosphatemia greater than 6.9 mg/dL [30]. These data reveal a substantial number of episodes of hypercalcemia and hyperphosphatemia with this treatment.

Calcimimetics

A new novel approach to decrease PTH secretion and control secondary hyperparathyroidism is through the stimulation of the calcium sensing receptor (CaR) in the parathyroid gland by new agents that mimic the effect of blood ionized Ca; these are the so-called calcimimetics. Early studies showed that calcimimetics are potent inhibitors of PTH secretion with rapid onset of action, over minutes to hours. Recent multicenter randomized studies have shown that a new generation of calcimimetics, AMG 073 (cinacalcet), in hemodialysis patients effectively suppresses PTH levels without inducing hypercalcemia or hyperphosphatemia. In fact, treatment with cinacalcet resulted in a significant decrease of Ca × P product. Thus, this compound, by directly targeting CaR in the parathyroid gland, may provide an alternative and/or an adjunct to vitamin D therapy in ESRD patients with secondary hyperparathyroidism and permit further suppression of PTH without increases in serum Ca or worsening of the hyperphosphatemia. Long-term studies evaluating cinacalcet therapy and follow-up are needed to determine if this compound(s) improves survival and the quality of life of ESRD patients.

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