New Therapies for Uremic Secondary Hyperparathyroidism

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Secondary hyperparathyroidism (SHPT) is a common and serious complication of chronic kidney disease (CKD). It affects more than 300,000 end-stage renal disease patients treated by dialysis and probably more than 3 million patients with CKD worldwide. For a long time, traditional therapies for SHPT had consisted of correcting the hypocalcemia using calcium salts and vitamin D derivatives, preventing the hyperphosphatemia by calcium- or aluminum-containing intestinal phosphate binders, and recently by using no metal-containing intestinal phosphate binders; however, these therapies are limited by the occurrence of hypercalcemia, hyperphosphatemia, and the lack of specificity and long-term efficacy. Moreover, surgical parathyroidectomy (PTX), which remains the gold standard therapy, is not exempt from risk. PTX exposes patients to anesthesia risks, presurgical and postsurgical complications, and in many cases a permanent state of hypoparathyroidism. Thus, the medical treatment of SHPT became an ideal target for the development of new therapies and strategies. The purpose of this article is to provide an overview of these new therapies, including vitamin D analogs, intestinal phosphate binders, calcimimetics, parathyroidectomies, tyrosine kinase inhibitors, azydothymidine, anticalcineurins, N-terminal truncated parathyroid hormone fragments, bisphosphonates, calcitonin, osteoprotegerin, and others. The use of these new therapies alone or in combination may help to optimize the future treatment of SHPT in CKD patients.

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arrhythmias, ischemia, and left ventricular failure in uremic patients. These abnormalities may also explain the inverse relationship found between serum PTH levels and mortality rate in dialysis patients.9

The prevention and control of SHPT has been a great challenge for all nephrologists since the beginning of renal replacement therapies, and now it has become more crucial because the PTH-related complications mentioned above and the recent recommendations made by the National Kidney Foundation–Kidney Disease Outcomes and Quality Initiative (NKF-K/DOQI).10 For a long time, the traditional therapies for SHPT had consisted of correcting the hypocalcemia using calcium salts and vitamin D derivatives, preventing the hyperphosphatemia using calcium- or aluminum-containing intestinal phosphate binders, and, recently, by using no metal-containing intestinal phosphate binders; however, these therapies are limited by the occurrence of hypercalcemia, hyperphosphatemia, and the lack of specificity and long-term efficacy. Moreover, surgical parathyroidectomy (PTX), which remains the gold standard therapy, it is not exempt from risk. PTX exposes patients to anesthesia risks, presurgical and postsurgical complications, and, in many cases, a permanent state of hypoparathyroidism.11 However, there have been tremendous developments in the medical treatment of SPTH, mainly because of insights derived from fundamental and clinical research. The purpose of this article is therefore to provide an overview of these therapeutic advances that may help to optimize the treatment of SPTH.

Correction of Biochemical Abnormalities Known to Favor the Development of Secondary Hyperparathyroidism

Vitamin D Deficiency

Reduced calcitriol synthesis by the diseased kidneys and by any extra renal source plays a major role in the pathogenesis of SHPT. In addition, plasma levels of 25-hydroxyvitamin D 25(OH)D 3 in patients with CKD are often reduced because of nutritional vitamin D deficiency, low sunlight exposure and loss of vitamin D in urine in patients who have nephrotic-range proteinuria or in the dialysis; fluid in patients who are treated with peritoneal dialysis. The biological consequences of vitamin D deficiency are multiple and comprise parathyroid gland dysfunction, reduced bone mineral density, and higher rate of bone fractures.12-15

Vitamin D and calcitriol act by binding to a nuclear receptor that contains two “zinc fingers” that mediate the binding of vitamin D–vitamin D receptor (VDR) to a regulatory promoter in DNA upstream regions of genes with a vitamin D-responsive element (VDRE). The binding of the vitamin D-VDR complex to the VDRE results in the transcription of specific mRNAs and the inhibition of the PTH gene expression. In CKD patients, there are impairments in the binding of vitamin D to VDR as well as in the binding of the vitamin D-VDR complex to the VDRE. Both of these events, in addition to the reduced number of VDRs on parathyroid, bone, and kidney cells, are responsible for the vitamin D-resistant state and a reduced serum total calcium level.16,17 Based on these findings, the NKF-K/DOQI had recommended that if serum levels of 25(OH)D 3 are lower than 30 ng/mL supplementation with vitamin D 2 should be initiated10 in patients with stages 3 and 4 of CKD. The levels of 25(OH)D 3 should be maintained in all uremic patients between 20 and 40 ng/mL.10

In addition to its effect on controlling PTH secretion, the administration of vitamin D seems to significantly improve the survival of CKD patients on dialysis, according to a large retrospective study compiling more than 50,000 patients in the United States.18,19

Certain new vitamin D analogs (Table 1) suppress PTH secretion with the same potency as calcitriol while showing fewer hypercalcemic and

Table 1. Vitamin D and Vitamin D Analogs for the Treatment of Secondary Hyperparathyroidism

| Vitamin D3 | Cholecalciferol or calcidiol |
| Vitamin D2 | Ergocalciferol |
| Active vitamin D derivatives | Calcitriol |
| | Paricalcitol or Zemplar (19-nor-1,25(OH)2D2) |
| | 22-oxa-calcitriol (OCT or Maxacalcitol) |
| Proactive vitamin D derivatives | Alfacalcidol |
| | 1α-(OH) vitamin D2 (doxercalciferol or Hectorol) |
| | Hexafluorocalcixal or falecalcitriol |
| | 24,25(OH)2D3 vitamin D3 |
hyperphosphatemic effects. The mechanisms for such selectivity are not established, but may include differences in the binding affinity for the VDR, in the enzymatic degradation by certain hydroxylases, and in the activation of genomic compared with rapid, nongenomic pathways via putative plasma membrane receptors. Many of these vitamin D analogs, including oxacalcitriol, paricalcitol, and doxercalciferol, are undergoing extensive experimental evaluation with the hope of obtaining the ideal vitamin D molecule that suppresses PTH with reduced or no effect on serum calcium and phosphate levels (Table 1).

Hypocalcemia

Hypocalcemia is the major posttranscription regulator of PTH secretion and parathyroid hyperplasia in CKD patients. Low extracellular calcium stimulates the expression and the synthesis of protective trans-acting factors that stabilize the PTH mRNA by binding to a minimal 63-nucleotide cis acting instability sequence in its mRNA 3'-untranslated region. Thus, the correction of hypocalcemia using calcium salts, including calcium carbonate and calcium acetate, is one of the first measures for preventing and treating SHPT as it has been largely revised by numerous investigators. Moreover, the NKF-K/DOQI emphasizes that in CKD patients (stages 3 and 4), the serum levels of corrected total calcium should be maintained within the normal range, whereas in patients in stage V or those treated by dialysis, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). The total daily intake of elemental calcium in CKD patients should not exceed 2,000 mg per day.

Hyperphosphatemia

A high extracellular concentration of phosphate also stimulates parathyroid cell proliferation and PTH secretion. Similar to hypocalcemia, phosphate regulates the PTH gene posttranscriptionally by regulating the binding of parathyroid cytosolic proteins, trans factors, to a defined cis sequence in the PTH mRNA 3'-untranslated region, thereby determining the stability of the transcript. Based on these findings and on the association between high serum phosphorus levels and cardiovascular mortality in dialysis patients, the NKF-K/DOQI also recommends maintaining serum phosphorus levels at or above 2.7 mg/dL (0.87 mmol/L) and no higher than 4.6 mg/dL (1.48 mmol/L) in CKD patients at stages 3 and 4. In CKD patients stage 5 and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L).

Effectively, decreasing phosphate intake has been shown for 5 decades to decrease PTH and to favor a positive calcium balance if the dietary calcium intake is simultaneously increased. It has also been shown that phosphate restriction with physiological calcium and vitamin D2 supplements not only suppressed PTH but also cured osteitis fibrosa and osteomalacia, without changing of the parathyroid calcium set point. Several controlled studies carried out in more than 1,000 patients have shown the efficacy of a variety of phosphate binders, including calcium carbonate, calcium acetate, aluminum hydroxide, calcium gluconate, calcium ketoglutarate, magnesium carbonate, and sevelamer HCL, in controlling serum phosphate levels in CKD and in dialysis patients. Other noncalcium-, aluminum-, and magnesium-containing phosphate binders are being evaluated as potential alternatives to classic agents such as lanthanum carbonate.

Chronic Metabolic Acidosis

Chronic metabolic acidosis (CMA) alters the homeostatic relationships between blood ionized calcium, PTH, and 1,25OH₂D₃ such that bone dissolution is exaggerated, bone mineral density is reduced, and bone fractures are common in acidoic CKD patients. Linear growth in children is reduced by CAM, and normalization of serum bicarbonate levels restored normal growth. Acidosis contributes to renal osteodystrophy in CKD patients, and its correction by a high bicarbonate concentration in the dialysis bath stops the progression or the worsening of SHPT. Therefore, serum bicarbonate levels should be maintained at >22 mmol/L in CKD patients, either with or without alkali salt supplementation, as recommended by the K/DOQI.

Controlling PTH Secretion at the Molecular Level

Enhancing VDR Expression in Parathyroid Glands

Hyperplastic and adenomatous parathyroid glands have reduced VDR expression, which plays an
important role in the setting of SHPT. The role of vitamin D in controlling PTH has been elegantly shown in mice ablated of the VDR gene \( \text{VDR}^{-/-} \). Homozygous mice \( \text{VDR}^{-/-} \) are phenotypically normal at birth and live normally at least until 6 months. They become hypocalcemic at 21 days of age, at which time their serum PTH levels begin to increase. Hyperparathyroidism is accompanied by an increase in the size of the parathyroid gland as well as an increase in PTH mRNA levels. Rickets and osteomalacia appear by day 35 of age. These mice also develop progressive alopecia from the age of 4 weeks. Interestingly, when \( \text{VDR}^{-/-} \) mice were fed a diet that prevents secondary hyperparathyroidism in vitamin D-deficient rats, this diet normalized growth and serum ionized calcium levels. Moreover, the correction of ionized calcium levels prevented the development of parathyroid hyperplasia and an increase in PTH messenger RNA expression and in serum PTH levels. \( \text{VDR}^{-/-} \) animals fed this calcium-rich diet did not develop rickets or osteomalacia. These studies suggested that normalization of mineral ion homeostasis and the activation of the CaR could prevent the development of hyperparathyroidism, osteomalacia, and rickets in the absence of the genomic actions of 1,25-dihydroxyvitamin D3. However, when crossing \( \text{VDR}^{-/-} \) mice with animals deficient for the gene encoding the 1,25(OH)2D3 synthesizing enzyme, the 25 hydroxyvitamin D-1alpha-hydroxylase \( \text{1a(OH)ase}^{-/-} \) enlarged parathyroid glands, which those mutants showed, could only be normalized by the combination of calcium and 1,25(OH)2D3, apparently independently of the VDR, indicating that calcium cannot entirely substitute for vitamin D in the control of parathyroid cell growth but that the two agents have discrete and overlapping functions. The vitamin D therapy also has the advantage of enhancing the expression of its own receptor, the VDR, in parathyroid glands, therefore potentializing its suppressive effect on PTH production.

### Enhancing CaR Expression in Parathyroid Glands

The CaR mRNA expression in parathyroid cells is downregulated in chronic renal failure, which contributes to the reduced response of these cells to serum calcium concentration and to the stimulation of PTH synthesis. This down-regulation is probably the result of a combination of factors, namely low serum calcium and vitamin D, and high phosphorus and uremic toxins (Table 2). Interestingly, the parathyroid CaR can be pharmacologically upregulated by the administration of calcimimetics and by calcium. This phenomenon may explain why patients with severe SHPT, with certainly nodular parathyroid tumors and reduced CaR, still respond satisfactorily to the calcimimetics treatment. The parathyroid CaR is also upregulated by age, probably in response to the usual decrease in the calcium and vitamin D balance observed with ageing. Interleukin 1 (IL-1), which is a well-known potent inhibitor of PTH secretion, exerts its effects by upregulating the parathyroid CaR.

### Table 2. Regulation of the CaR mRNA Expression in Parathyroid Cells

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Age</td>
<td>Increase</td>
</tr>
<tr>
<td>Calcimimetics</td>
<td>Increase</td>
</tr>
<tr>
<td>Calcium</td>
<td>Increase</td>
</tr>
<tr>
<td>Interleukin 1</td>
<td>Decrease</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Decrease</td>
</tr>
<tr>
<td>Uremic toxins</td>
<td>Decrease</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Increase</td>
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</table>

The CaR of the parathyroid gland is the principal regulator of PTH secretion. When serum calcium decreases, the CaR is inhibited and PTH-containing vesicles move to the cell membrane and release PTH to the circulation. When serum calcium increases, the CaR is activated and the release of PTH is inhibited. There is a sigmoid relationship between the secretion of PTH and the serum calcium concentration, which led to the definition of a calcium set point. This is the ionized serum calcium concentration corresponding to a serum PTH value intermediate between the maximal and minimal stimulated PTH values (midrange value). The value of the set point in subjects with normal parathyroid function is between 1.10 and 1.20 mM.

The calcium setpoint has been found increased, in in vitro studies using dispersed parathyroid cells from uremic patients, as well as in in vivo studies in patients with primary hyperparathyroidism. However, in patients with SHPT, there have been conflicting results regarding the
calcium set point for several investigators it is abnormally increased, 47-49 for others it is normal. 50-54 The regulation of the set point by vitamin D therapy is also a controversial issue; we did not find any improvement of the sensitivity of parathyroid cells to calcium after 1 year of vitamin D treatment. 55,56 However, the differences in the results obtained in in vivo studies probably reflect the lack of a standardized methodology. In some studies, serum total calcium concentration was used instead of the biologically more important ionized calcium concentration. In other studies, the variations in serum calcium concentration were obtained by manipulating the calcium concentration in the dialysis bath instead of infusing citrate, EDTA (ethylenedinitrilotetraacetate), or calcium. 53,57,58 and finally, diverse mathematical models have been used to construct the calcium-PTH curve. Nonetheless, most of the in vivo findings support the contention that the set point for calcium-regulated PTH secretion is greater than normal in patients with uremic SHPT mainly because of a reduced sensitivity of the parathyroid CaR to extracellular calcium. 53,57,60

The calcimimetics are phenylalkaline compounds that increase the intracellular calcium concentration and inhibit PTH secretion at nanomolar concentrations in bovine parathyroid cells, in Xenopus laevis oocytes expressing the bovine or human CaR, and in HEK 293 cells transfected with the CaR. They also potentiate the effect of extracellular calcium on the CaR but do not have any effect in the absence of extracellular calcium. By increasing the sensitivity of the CaR to extracellular calcium, they shifted the concentration response curves for extracellular calcium to the left and reduced the set point for calcium-regulated PTH secretion in in vitro studies. 61,62 The steepness of the sigmoid curve becomes also more abrupt, indicating an increase in the sensitivity of the CaR to extracellular calcium and a more rapid response of the parathyroid cells to changes in the extracellular calcium concentration. It is therefore plausible that these compounds will also decrease the calcium set point in in vivo studies; however, no data have been reported yet, either in animals or in subjects with primary or secondary hyperparathyroidism.

There is now convincing evidence showing that calcimimetics can efficiently control in the short term (26 weeks) and in the long term (≥3 years) and probably stop the progression of SHPT in CKD patients treated with dialysis. 63 Cinacalcet HCL (Sensipar), which has been the most extensively studied second-generation calcimimetic, has been approved in the United States by the Food and Drug Administration, and now in the Europe by the European Medicines Agency (EMEA), for the treatment of SHPT (serum PTH level >300 pg/mL) in dialysis patients and hypercalcemia in patients with parathyroid carcinoma.

Phase I and II studies with the second-generation calcimimetic cinacalcet HCL in dialysis patients with SHPT started in 1998, and some of these patients actually have been treated for more than 6 years. Based on these studies and in pharmacokinetic studies, it has been possible to define the optimal oral doses of cinacalcet HCL (30 to 180 mg/d) and the usual responses, in terms of serum PTH and corrected total calcium, in dialysis patients with SHPT. 64 Independently of the basal serum PTH value, PTH decreases 60% to 70% 2 to 4 hours after the administration of cinacalcet HCL and stays significantly lower than the baseline value 24 hours later. Serum total calcium, corrected for albumin concentration, follows the same trend as PTH but delayed by 2 to 4 hours; it can decrease by 20% to 30% of the basal value. The marked reduction in serum PTH (24-hour postcinacalcet administration) seen during the 12-week titration phase can attain up to 90% of the baseline value, similar to a chemical parathyroidectomy. During this phase, the decrease in PTH is also accompanied by a transient, hypocalemia, which is in part due to a phenomenon of “hungry bone syndrome” similar to that observed after a surgical parathyroidectomy, 65 and also to a decrease in the intestinal calcium absorption secondary to a diminished expression of the TRPV-5 calcium transporter. 66 Its correction requires a transient increase in the dietary calcium intake or the prescription of high doses of calcium salts alone or in combination with vitamin D.

The combined results of three 12-week, randomized, double-blind, placebo versus cinacalcet HCL, phase II clinical trials, carried out in 215 hemodialysis patients, were reported in 2001. 67 The cinacalcet HCL doses were titrated up to 50 mg/d in 2 studies, and 100 mg/d in 1 study, always based on PTH levels and safety profile. Mean serum PTH levels were reduced by 20% to 33% in the cinacalcet HCL group and increased
by 16% in the placebo group. Eighty-three percent of cinacalcet HCL patients had a reduction in serum PTH levels >30% at the end of the 12 weeks. Mean serum calcium × phosphorus product decreased by 28% in the cinacalcet HCL group and increased by 30% in the placebo group.

In several phase III studies, cinacalcet HCL at doses of 20 to 180 mg/d reduced mean serum PTH levels of 33% and 65% after 18 weeks and 3 years of treatment, respectively. Mean serum calcium × phosphorus product decreased by 28% in the cinacalcet HCL group and increased by 30% in the placebo group.

In the long term, 2 reports have shown that cinacalcet effectively sustained reductions in PTH for up to 3 years without increasing concentrations of serum calcium, phosphorus, or calcium-phosphorus product.

A combined post-hoc analysis of clinical events using data from 4 (n = 1,184 patients) cinacalcet HCL registrational (phase II and III) studies suggests that cinacalcet HCL has a beneficial effect on rates of PTH, fractures, and hospitalization for cardiovascular complications.

Seventeen percent of patients with kidney transplants have a persistent SHPT and hypercalcemia, often requiring surgical parathyroidectomy. The efficacy and safety of cinacalcet HCL in reducing and controlling PTH and the hypercalcemia has been recently assessed in 2 clinical studies. Twenty-five renal allograft recipients with persistent SHPT were treated for at least 3 months with a mean dose of 30 mg/d of cinacalcet HCL. All patients showed a significant reduction in serum PTH and calcium. They became normocalcemic (2.10 to 2.60 mmol/L) within the first 2 to 3 weeks of treatment, and they maintained it throughout the study.

Parathyroid carcinoma is a rare cause of hypercalcemia attributable to excessive PTH secretion. Its medical treatment is a real challenge because these tumors are often resistant to chemotherapy and radiotherapy. Two recent studies in 40 patients with inoperable parathyroid carcinoma and serum calcium levels between 14.5 and 15.4 mg/dL have shown that 30 to 90 mg 4 times per day of cinacalcet HCL reduced mean serum calcium to 11.8 mg/dL and maintained this reduction for up to 3 years.

The most frequent side effects of cinacalcet HCL treatment are gastrointestinal troubles, namely nausea, gastralgia, and vomiting. The incidence of other side effects is not greater in dialysis patients receiving cinacalcet HCL than in nontreated patients. There were also transient episodes of hypocalcaemia in 5% of cinacalcet HCL patients versus 1% of placebo patients. However, these episodes were rarely associated with symptoms and could be rapidly corrected by increasing the prescription of calcium salts or vitamin D. These episodes of hypocalcaemia can be prevented by a close monitoring of serum calcium during the first weeks of treatment, and in particular in patients with history of cardiac arrhythmias and seizures because their threshold could be decreased.

Altogether, the results of these clinical studies reinforce the hypothesis that targeting and activating the parathyroid CaR by calcimimetics is a specific way to efficiently treat SHPT in CKD patients.

**Activating Autoantibodies Specifically Directed Against the CaR**

It has now been shown that the CaR may be one of the targets of cellular and humoral immunity in idiopathic autoimmune hypoparathyroidism. There are autoantibodies that inactivate the calcium-sensing receptor and lead to a syndrome very similar to familial hypocalciuric hypercalcemia. In other cases, patients with multiple
autoimmune disorders can have specific autoantibodies directed against the CaR, associated with an intermittent, relapsing hypercalcemia and elevated serum PTH levels, which can be responsive to glucocorticoids. When the parathyroid glands of these patients are surgically removed, they show an inflammatory involvement. These cases differ from familial hypocalciuric hypercalcemia because the serum calcium level can be entirely normal and because the elevations in the serum calcium and PTH levels respond to glucocorticoids.

It has also been learned that autoantibodies may functionally activate the CaR in idiopathic hypoparathyroidism in a scenario parallel to the autoimmune activation of thyrotropin receptors in Graves disease. Generally, these autoantibodies are of the immunoglobulin G type, which do not involve the activation of the complement cascade and do not result in the destruction of parathyroid cells. They only interfere with CaR binding sites and modulate its activity. The use of these kinds of antibodies could be another way to target the parathyroid CaR and to treat either hypofunctioning or hyperfunctioning parathyroid states.

Reducing Parathyroid Cell Number and Function

Parathyroidectomies

PTX continues to be required in a subset of patients with SHPT. Its indications are still not well defined, and there are no studies to define absolute biochemical criteria that would predict whether medical therapy will not be effective and surgery is required to control SHPT. There has been some suggestion that in those patients with a large parathyroid mass attempts at medical therapy, might fail and therefore, assessments of parathyroid mass with ultrasonographic or radionuclide techniques could conceivably be useful as predictors of the efficacy of medical therapy. Unfortunately, there is insufficient evidence to support this at the present time. Several types of surgery can be performed; whereas subtotal parathyroidectomy or total parathyroidectomy with or without autotransplantation have all been shown to be successful, there are no comparative studies. Efficacy and recurrence rates seem to be comparable.

Moreover, with the dramatic improvement of parathyroid localization by new ultrasound and radionuclide techniques and the use of intraoperative serum PTH measurements, it will be possible to perform minimally invasive surgery a sort of partial, targeted, unilateral parathyroidectomy to remove, with only local anaesthesia, the most active parathyroid tumor, which may help in controlling severe SHPT in patients resistant to calcimimetic therapy. This change of attitude is actually taking place for surgery in the case of primary hyperparathyroidism, and it will be supported by the arrival of new endoscopic techniques.

An alternative to surgical PTX is the destruction of parathyroid tissue by direct injection of alcohol into the parathyroid gland under ultrasound guidance, or with direct injection into the parathyroid gland of a vitamin D derivative such as calcitriol and oxacalcitriol alone or in combination with calcimimetics. However, further studies with this technique are needed to evaluate its role in long-term therapy.

Selective Inhibition of Parathyroid Cell Proliferation by Tyrosine Kinase Inhibitors

Parathyroid hyperplasia in CKD patients is associated with enhanced expression of transforming growth factor-alpha (TGFα), which acts on a normally expressed receptor (EGFR). In animal models, the enhancement in parathyroid weight and proliferation activity, induced by 5/6 nephrectomy and exacerbated by high-phosphorus and low-calcium diets, is associated with a 2- to 3-fold increase in TGFα and EGFR content in parathyroid cells. In these models, the prevention of the increase in both TGFα and EGFR parallels the efficacy of either phosphate restriction or high calcium intake in ameliorating the parathyroid hyperplasia. Moreover, suppression of TGFα/EGFR signaling through prophylactic administration of potent and highly selective inhibitors of ligand-induced EGFR activation (AG-1478, TKI) or of the EGF-R (ZD-6126), completely prevented both high-phosphate and low-calcium–induced parathyroid hyperplasia.

Azidothymidine

Zidovudine, 3’-azido-3’-deoxythymidine (AZT), is a thymidine analog originally developed as an
antineoplastic agent with biological activity in patients with solid tumors.\(^9^6\) It can be incorporated into viral DNA and acts as a false substitute for the viral reverse transcriptase, blocking chain elongation, preferentially at the telomeric ends of chromosomes in proliferating cells. For this, AZT is used almost exclusively as an antiretroviral agent in the therapy of AIDS. AZT also has multiple pharmacologic actions. When human parathyroid cells removed from patients with parathyroid carcinoma were exposed in vitro to AZT, they showed an intracellular accumulation of AZT-monophosphate and inhibition of telomerase, which correlate with the inhibition of cell proliferation. In addition, AZT seems to increase the apoptotic rate of these cells and had no effect in noncarcinoma human adenomatous parathyroid cells in culture. It has therefore been suggested that AZT in association with calcimimetics, respectively acting on inhibition of parathyroid cell proliferation rate and PTH secretion, could reduce the severity of the biological and clinical progression of parathyroid carcinoma.\(^9^7\)

**Specific Immunosuppression: Anticalcineurins**

Scarce information exists regarding a potential selective antiproliferative effect of anticalcineurins on parathyroid cells. Mice with genetic deletion of the calcineurin \(A^\beta\) gene show a marked increase of the expression of the PTH mRNA that is still regulated by low-extracellular-calcium and high-phosphate diets. Moreover, cyclosporine A, which is a calcineurin inhibitor, is known to regulate posttranslationally the AUFI protein and thereby the stability of the PTH mRNA through the cis sequence in the PTH mRNA 3'-untranslated region.\(^9^8\) However, additional studies are needed to assess whether calcineurin inhibitor treatment in CKD patients or in renal transplant recipients shows reduced serum PTH levels or smaller parathyroid glands than in those without.

**Blocking PTH Biological Actions**

**N-Terminal Truncated PTH Fragments as Inhibitors of the PTH Receptor**

Bioactive 1–84 PTH is encoded by a gene on the short arm of chromosome 11, which, before giving rise to this mature peptide, encodes a 115-amino-acids (aa) peptide called pre-pro-PTH (pre(25 aa)-pro(6 aa) peptide). Most of the 1–84 PTH is degraded by proteolysis in the cytosol before it can be secreted. A major proteolytic product, the 7–84 PTH fragment, is found in the circulation as well as in the cytoplasm of parathyroid cells.\(^9^9\) This fragment, along with other C-terminal PTH fragments, has long been considered biologically inert; however, recent developments of new immunoradiometric assays for PTH and research on the PTH receptors suggest that 7–84 and other N-truncated PTH fragments may have important biological functions.\(^1^0^0\)–\(^1^0^3\) For example, thyroparathyroidectomized rats fed a 0.02%-calcium diet show a significant increase in serum calcium after treatment with hPTH(1–84). In contrast, hPTH(7–84) produced a slight but significant decrease in serum calcium. When both peptides are given together in a 1:1 molar ratio, the calcemic response induced by hPTH(1–84) was reduced by 94%.\(^1^0^3\) Therefore, there is convincing evidence of the anticalcemic actions of 7–84 PTH and of other shorter C-terminal PTH fragments incapable of activating the classical type I PTH receptor. Such peptides also can exert antiresorptive and antiosseoclastogenic effects in vitro, which further suggests the existence of functional receptors for C-terminal PTH molecules. To date, no experimental animal or human studies have been performed to test the effect of the administration of any these C-terminal PTH fragments in the control of SHPT or the hypercalcemia associated with SHPT. However, indirect insights have been obtained from the modulation of the ratio PTH(1–84)/PTH(7–84) by medical therapies. For instance, intravenous administration of vitamin D has been shown to reduce the ratio PTH(1–84)/PTH(7–84) in hemodialysis patients with SHPT.\(^1^0^4\) However, the clinical and biological relevance, as well as the impact on bone turnover of such a treatment in CKD patients, cannot yet be predicted.

**Human Antibodies Against PTH**

Using antibodies against PTH would be an interesting way to transiently halt the deleterious effects of PTH on its classical target organs, bone and kidney, and on other organs so far considered nonclassic. It could serve to momentarily control hypercalcemia and hyperphosphatemia while waiting for a surgical or nonsurgical correction of
SHPT. However, what has been observed with the use of these antibodies is more than surprising. The treatment of severe hyperparathyroidism secondary to parathyroid cancer with ABX10241, a fully human monoclonal antibody generated using XenoMOuse, intravenously administered, significantly and dose-dependently reduced serum unbound PTH. This reduction in PTH is associated with a decrease in serum calcium and collagen type I N-telopeptides. No human antibodies or antihuman PTH antibodies have been detected after 6 months of treatment at doses ranging from 25 to 500 mg per week. ABX10241 also seems to be efficient in reducing serum PTH in CKD hemodialysis patients with SHPT.

**Bisphosphonates**

Bisphosphonates are synthetic compounds industrially used for more than a century in the inhibition of calcium-carbonate precipitation. They have a particular tropism to mineral, a property that directs bisphosphonates to deposit in the skeleton where they act by becoming metabolized by osteoclast cells to toxic analogs of ATP or by inhibiting farnesyl diphosphate synthase. In certain patients with nonsuppressible SHPT who are unsuitable for or are waiting for PTX, intravenous bisphosphonates may be indicated to control hypercalcemia. Because the high bone turnover induced by SHPT also increases phosphate efflux from bone, the use of bisphosphonates may also help to control hyperphosphatemia in these patients. Another indication of bisphosphonates may be when patients with SHPT show a severe and progressive bone loss, as can be assessed by bone mineral density. There are few risks with the administration of intravenous bisphosphonates at the appropriate dose to dialysis patients.

**Calcitonin**

Calcitonin (CT) is a 32-amino-acid peptide produced primarily by thyroid C cells and regulated by the same CaR as the one for parathyroid cells. The main effect of CT is to inhibit osteoclast-mediated bone resorption; it causes a dramatic decrease in osteoclast size and in its bone-resorbing activity through the stimulation of intracellular cyclic adenosine triphosphate (cAMP) accumulation. CT administration has a modest and rapid effect on lowering serum calcium in hypercalcemic patients. Unfortunately, repeated exposure to CT leads to downregulation of its receptor on osteoclast cells, and most patients who initially are responders to CT become resistant to its hypocalcemic effects. Nonetheless, CT treatment has been tested in CKD patients with SHPT since the 1970s. In some of these studies, the combined therapy with CT and vitamin D seemed to be more effective than vitamin D alone in inhibiting bone resorption and in increasing bone mineral density in hemodialysis patients with SHPT. There is possibly an indication for the use of CT as an osteoclast inhibitor in certain situations in which treatment with vitamin D derivatives is associated with direct stimulation of osteoclastic resorption and blockage of bone formation.

**Osteoprotegerin**

Osteoprotegerin (OPG) is a soluble circulating protein member of the tumor necrosis factor receptor family. It has a profound inhibitory effect on osteoclastogenesis and bone resorption by binding to the receptor activator of the nuclear factor kappa B ligand. Serum OPG levels are significantly increased in CKD dialysis patients compared with normal subjects, and they are 2 to 3-fold higher in dialysis patients with SHPT than in those with low serum PTH levels. A rapid progression of vascular calcification has also been associated with high serum OPG levels. Thus, OPG might protect bone against intensive bone demineralization induced by SHPT in dialysis patients; however, its precise role and the mechanisms by which it does this remain to be established. Nevertheless, a recent report shows that the administration of human recombinant OPG to patients with juvenile Paget disease, a genetic bone disorder characterized by high bone turnover, suppresses bone resorption efficiently and improves bone quality. The advent of this new recombinant OPG might offer another alternative for controlling bone resorption in CKD patients with SHPT.

**Others**

Using antibodies against type-I PTH receptor (PTHR-I) would be an interesting way to transiently halt the deleterious effects of PTH on its classic target organs, bone and kidney, and other nonclassic PTH target organs. However, there is no such antibody available for clinical use so far.
Another member of the PTH family could also show some anti-PTH-I activity; TIP-39 (tuberoinfundibular peptide 39) is a protein produced by the hypothalamus and the pancreas that binds and activates the type-II PTH receptor (PTH-R-II). What is interesting is that TIP-39 also binds the PTHR-I without inducing any stimulation. This property may render this peptide useful as a PTHR-I antagonist in case of resistant SHPT.

Conclusions

This review shows the tremendous evolution in the medical treatment of SHPT in CKD patients. There is a hope that these new therapies will help to optimize the treatment of SHPT and will reduce many of the serious skeletal and vascular complications of SHPT in CKD, dialysis, and kidney transplant patients. However, long-term studies are needed to evaluate the efficacy and potential beneficial effects on mortality rate, skeletal fracture incidence, and prevention of cardiovascular morbidity for many of these therapies.

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