Review Article

Secondary and Tertiary Hyperparathyroidism in Chronic Kidney Disease: An Endocrine and Renal Perspective

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Abstract

Secondary Hyperparathyroidism (SHP) seen as a frequent complication in Chronic Kidney Disease (CKD) has many pathogenetic peculiarities that are still incompletely defined and understood. During the long course of chronic renal failure, SHP can also transform sometimes into the hypercalcemic state characterized by quasi-autonomous production of Parathyroid Hormone from the parathyroid glands: a disorder that is termed Tertiary Hyperparathyroidism. The clinical consequences of SHP in CKD are protean, encompassing bone and mineral abnormalities but as recently identified, also several metabolic and cardiovascular problems, the most important of which is vascular calcification. There have been several advances in the therapeutic armamentarium available for the treatment of SHP, though clear demonstration of a benefit regarding major clinical outcomes with any of the new agents is still lacking. This narrative review summarizes the current understanding about this disorder and highlights some of the recent research on the subject.

Keywords: CKD, FGF-23, parathyroid hyperplasia, renal failure, secondary hyperparathyroidism, tertiary hyperparathyroidism

Introduction

The parathyroid gland(s) play a pivotal role in bone mineral homeostasis through its secretion of parathyroid hormone (PTH). PTH increases calcium efflux from the bone, increases tubular reabsorption of calcium and phosphate excretion in the kidneys, and by stimulating the renal production of 1,25 dihydroxy vitamin D [(1,25 $(OH)_2D$], increases gastrointestinal absorption of calcium.

It is important to distinguish between a primary disorder of the parathyroid glands in which there is dysregulated and excessive production of PTH (as in the case of primary hyperparathyroidism, PHPT), and situations in which the parathyroid glands respond secondarily to a stimulus such as malabsorption or renal failure and reacts by increasing PTH secretion. These latter forms of hyperparathyroidism are collectively known as secondary hyperparathyroidism (SHP) [Table 1].

Tertiary hyperparathyroidism refers to the hypercalcemic state in which, after longstanding SHP, the stimulated parathyroid glands assume a quasiautonomous role akin to that seen in PHPT. The differentiation of tertiary from PHPT is usually made possible since in the former; a clearly identifiable longstanding disorder such as malabsorption or renal failure is present predating the onset of hypercalcemia [Table 2].

Though SHP and its eventual progression to tertiary hyperparathyroidism has many causes as outlined in Table 1, this review will focus on the pathogenic, clinical and therapeutic aspects of these conditions in the setting of chronic kidney disease (CKD).

The SHP associated with CKD is characterized by a complicated, multifaceted and as, yet incompletely understood pathophysiology. It is estimated that 30%-50% of stage 5 CKD patients have iPTH levels of >300 pg/ml.[1] As the kidneys fail, gross derangements in fluid and solute clearance occur. An initial adaptive response, it becomes maladaptive over time and leads to the clinical syndrome termed as Chronic Kidney Disease-Metabolic Bone disorder (CKD-MBD),[2] defined as a

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Table 1: Causes of secondary hyperparathyroidism

Chronic Kidney Disease
Decreased Calcium Intake
Decreased Absorption of Calcium
Vitamin D deficiency
Bariatric Surgery
Celiac disease
Pancreatic diseases with fat malabsorption
Renal Calcium losses
-Idiopathic hypercalciuria
-Loop Diuretics
Secondary to Phosphate Replacement therapy in conditions such as X-linked Hypophosphatemia, Autosomal Dominant Hypophosphatemia, Tumour Induced Osteomalacia etc.

systemic disorder of mineral and bone metabolism, manifested by either one or a combination of the following:

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

Normal physiology

The secretion of PTH is closely regulated by extracellular ionized calcium through the calcium sensing receptor (CaSR) on parathyroid cells.[3] PTH synthesis and secretion are also influenced by 1,25 $(OH)_2D$ produced in renal proximal tubular cells by the conversion of 25(OH)D under the influence of the enzyme 1-alpha hydroxylase. 1,25 $(OH)_2D$ binds to the vitamin D receptor (VDR) in parathyroid tissue and inhibits PTH mRNA synthesis.[4] Inorganic Phosphate (Pi) may also act as an important regulator of PTH although the exact sensing mechanism through which it does this still remains to be elucidated. In addition, the relatively recently identified and characterized fibroblast growth factor 23 (FGF-23), an osteocyte and osteoblast derived phosphaturic hormone[5] has been shown to decrease PTH synthesis and secretion[6] by acting on the parathyroid glands through its receptor Klotho-FGF.[7,8]

Pathophysiology

It was long considered that the failure of the kidney to excrete serum phosphate with resultant hyperphosphatemia is the key driver of SHP in CKD patients.[9] The formation of calciumphosphate salts with a reduction in serumionized calcium,[10] the inhibitory effect of Pi on the enzyme CYP27B1 (25(OH) D1alpha hydroxylase) that is involved in the conversion of 25hydroxy D to 1,25(OH)2 D in the proximal renal tubular cell[11] and the decreased viable renal mass.[12,13] in chronic renal insufficiency with resultant lesser 1alpha hydroxylase activity, all are believed to result in hypocalcemia and initiate the cascade of events that leads to dysregulation of parathyroid hormone in SHP. However, these postulations do not explain the clinical observation that serum 1,25$(OH)_2D$ begins to decline even in early kidney disease before overt hyperphosphatemia develops and that hyperparathyroidism develops early in chronic renal failure at a time when plasma calcium and phosphorous are within normal limits.

The identification and characterization of FGF-23 in the last decade has provided important clues towards understanding the early phases in the pathogenesis of SHP.[14,15] This 22.5 kDa protein, encoded by the FGF-23 gene located on chromosome 12 is secreted mainly by osteocytes and osteoblasts. Its synthesis and release is mainly stimulated by 1,25$(OH)_2D$ and also by Pi, PTH and calcium by as yet incompletely defined mechanisms though it is thought that PTH induces FGF-23 transcription through activation of the orphan receptor Nurr1 and through activation of PKA and Wnt signaling in bones thereby constituting a bone-parathyroid-endocrine loop.[16-18] FGF23 together with its obligate coreceptor, the membrane bound αKlotho function to induce phosphaturia through downregulation of sodiumphosphate cotransporters. The FGF-23 αKlotho complex also inhibits 1,25$(OH)_2D$ synthesis in the kidney by inhibiting 1alpha hydroxylase and, by stimulating 24hydroxylase, the catabolism of active vitamin sterols.[19] This leads to hypocalcemia and stimulation of the parathyroid gland [Figure 1]. A soluble and circulating form of αKlotho produced mainly by the kidney may also have additional autonomous (i.e., independent of FGF-23) phosphaturic and anti-calciuric effects.[20] A progressive renal reduction in production of both membrane-bound and circulating αklotho, increasing levels of FGF-23 secondary to its reduced renal clearance and due to Pi retention, and resistance to the phosphaturic effect of FGF-23 due to deficiency of αKlotho characterize CKD progression.

As FGF-23 level increases, a "trade-off" occurs between maintaining normophosphatemia versus 1,25 hydroxy vitamin D deficiency, with the latter progressing relentlessly and causing SHP.[21] Phosphate level will start to rise only when the adaptive compensation by FGF-23 becomes inadequate. At this stage, hyperphosphatemia, continued decreased 1,25$(OH)_2D$ and hypocalcemia all contribute to increasing PTH mRNA levels and PTH synthesis. Initial diffuse parathyroid cell hyperplasia and ultimately nodular hyperplasia results. A separate CaSR independent mechanism for hypocalcemia to stimulate PTH secretion may also be through microRNA (miRNA) dysregulation within the parathyroid glands.[22]

Though conflicting data also exists,[23] FGF-23 may also act directly on the parathyroid gland to suppress PTH secretion through the Klotho–FGFR1 complex.[24] In patients with advanced SHP, the parathyroid expression of the Klotho–FGFR1 complex is downregulated.[25] This likely contributes to the resistance to the inhibitory effect of FGF-23 on PTH secretion in progressive and advanced SHP.

As parathyroid hyperplasia progresses, both CaSR and VDR on the parathyroid glands become downregulated and reduced expression of these has been observed in the most severe forms

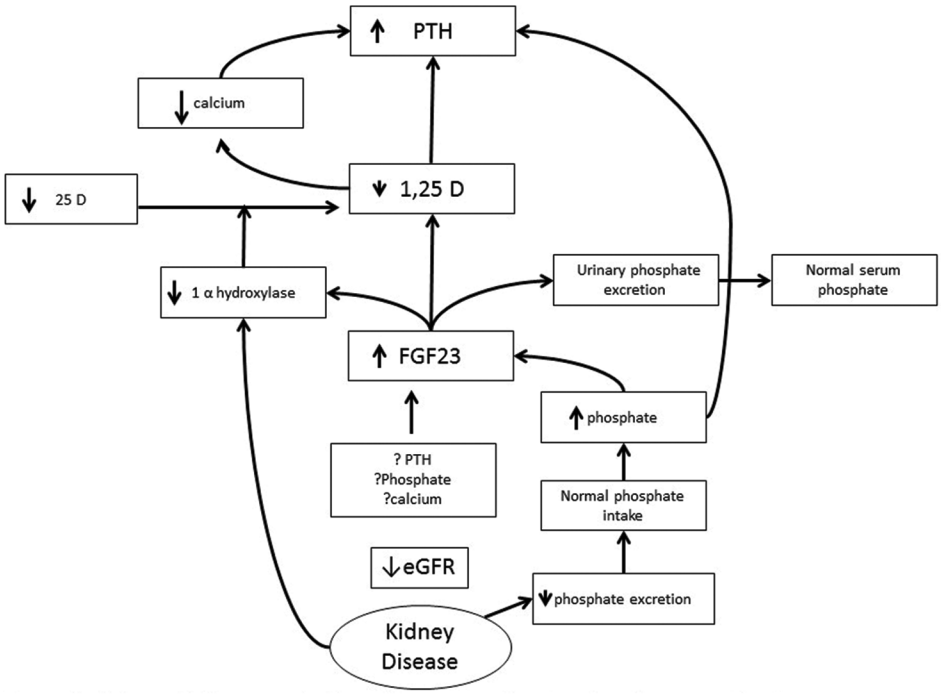

Figure 1: Schematic representation of the current understanding regarding the pathophysiology of SHP

of SHP.[26-30] The size of the parathyroid glands progressively increases as SHP worsens and gland size is positively correlated with serum PTH levels [Figure 2]. The cellular etiology of tertiary hyperparathyroidism is unknown, but it is postulated to be due to a monoclonal expansion of parathyroid cells in which the set point of the CaSRs has been altered such that semi-autonomous secretion of PTH occurs despite high serum calcium levels. Monoclonal chief cell growth results in the formation of nodules. Nodular glands have less VDRs and CaSRs[26-30] compared to diffusely hyperplastic glands and this exacerbates parathyroid gland resistance to calcitriol and calcium.

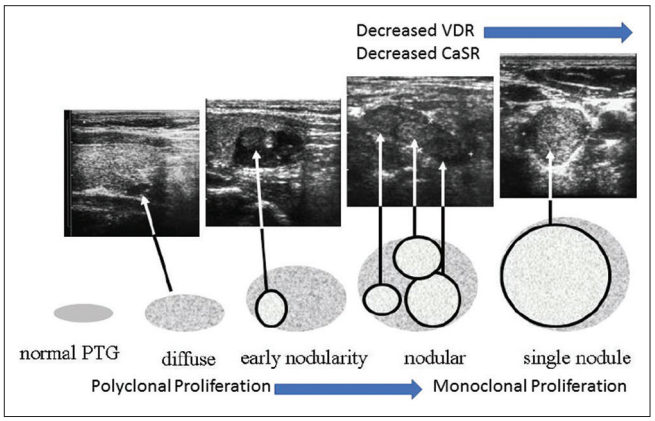

Figure 2: The stages in the evolution of secondary and tertiary hyperparathyroidism

Clinical Features

Skeletal manifestations

PTH binds to the PTH/PTHrP receptor on osteoblasts and thus by indirectly stimulating osteoclastic activity leads to a high turnover bone disease. Fragility fractures have been reported to be 2-4 times more frequent in patients with SHP when compared with age- and gender-matched normal populations. This increased risk is associated with an increased risk of mortality[31] and an association between PTH levels and fracture risk has been observed, with intact PTH levels above 900 pg/ml shown to be independently associated with an increased risk of incident fractures in the DOPPS study.[32] It has to be remembered however that the bone fragility in CKD may have several causes other than SHP; such as metabolic acidosis, anemia, hypogonadism, inflammation, beta 2 microglobulin associated amyloidosis, vitamin D deficiency, bone formation inhibition secondary to Wnt inhibition in osteocytes, etc. to name a few.

Extra-skeletal manifestations

Elevated PTH levels may be associated with an increased sympathetic drive, and endothelial stress and SHP may play a causal role in the development of vascular calcifications, ischemic cardiovascular events and cardiac failure.[33] In contrast to the intimal calcification seen in aging individuals with normal renal function, what is seen in patients with CKD is calcification of the medial layer.

Elevated PTH levels have been found to be independently associated with anemia, which is a hallmark of CKD and severe SHP is associated with a resistance to erythropoietin therapy in CKD.[34] It should be borne in mind that, no clear causal relationship between SHP and these extra-skeletal manifestations has been established, neither has it been

shown that correction of SHP can result in a complete remission of these clinical conditions.

Clinical Evaluation

The diagnoses of secondary and tertiary hyperparathyroidism are purely biochemical and therefore, accurate measurement of PTH is essential. PTH is a hormone of 84 amino acids. Over the last few decades, three generations of PTH assays have been developed that measure different parts of the molecule [Figure 3]. The first radioimmunoassay for PTH was developed in 1963 by generating a single polyclonal antibody against epitopes in the carboxy terminal (C terminal) end of the PTH molecule.[35] The first-generation assays had poor specificity as the antibodies used mainly targeted the non-bioactive portion of the PTH molecule; the C-terminal which is retained in CKD. The second-generation assays that were developed to overcome this problem use two sets of antibodies: (a) capture antibodies against epitopes located within the C-terminal and (b) detection antibodies directed to amino acid sequences 12-20 within the amino terminal end.[36] This assay is currently the most widely used and is called intact PTH assay (iPTH) as it is assumed that it captures intact PTH 1-84. However, the detection antibodies have been found to cross-react with PTH 7-84 fragments that also tend to accumulate in patients with CKD.[37,38] It has also become apparent that high concentrations of 7-84 PTH and some other C-terminal PTH fragments may oppose the biochemical and bone-metabolic effects of 1-84 PTH; aggravating the potential undesirable clinical consequences of overestimating 1-84 PTH concentrations in renal failure patients,[39,40] that is, the physician might mistakenly assume the erroneously high PTH reading as the correct value and may institute further PTH lowering therapies with disastrous consequences. To overcome these shortcomings, third-generation PTH assays such as the whole PTH assay and the Bio-Intact PTH assay have been developed.[41] Though the capture antibody used in the third-generation assay is the same as that used in the second-generation assay, the detection antibody used is directed towards the first four amino acids. These assays do not thus recognize 7-84 PTH and are therefore considered more specific to 1-84 PTH than second-generation assays. Two automated third-generation PTH assays are now available.[42] However, there is little evidence to show that they provide any better clinical information than the second-generation assays with regard to the diagnosis of CKD-MBD[43] and therefore have not been adopted for use in current guidelines for management of SHP. In general, PTH levels measured with second-generation assays are higher than those obtained with third-generation ones. The ratio of whole (biointact) to intact PTH levels has been noted to be between 0.6-0.7 in dialysis patients,[44] though exceptions to this rule have been reported in patients with severe SHP with a new molecular form of PTH with an intact N-terminus[45,46] that can be detected by third-generation PTH assays but not by second-generation ones identified in these patients. Thus in these patients, PTH levels measured with third-generation assays are paradoxically higher than those with second-generation ones. Existing clinical data suggest that an over-production of N-PTH may be associated with rapid progression of SHP and that N-PTH has significant bio-activity.[47,48]

Table 2: Biochemical differentiation between primary, secondary and tertiary hyperparathyroidism

Biochemical Parameter	Primary hyperparathyroidism	Secondary hyperparathyroidism	Tertiary hyperparathyroidism
Calcium	↑	↓	↑
phosphate	↓	↑*	↑
iPTH	↑	↑	↑

*N.B. SHP in patients with normal renal function (unlike as in those with CKD) is usually associated with low levels of phosphate given the inhibitory effect of PTH on Sodium-Phosphate co-transporters in the renal tubules

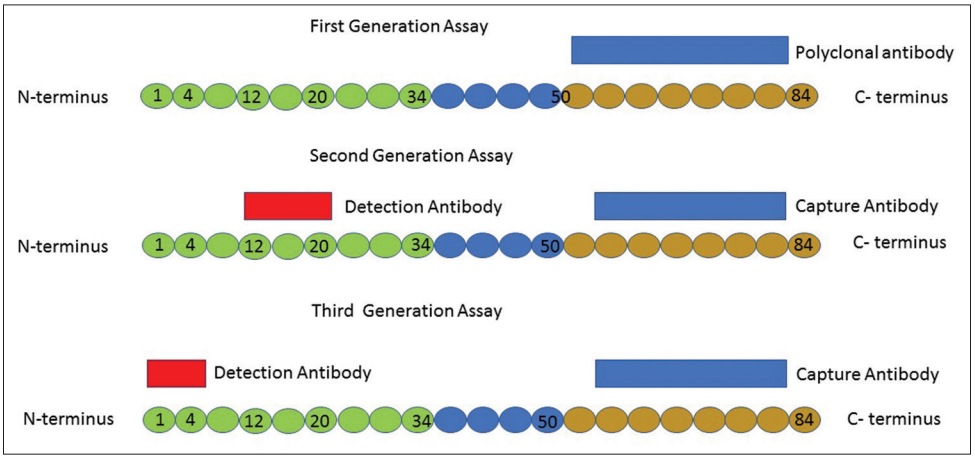

Figure 3: Schematic representation of the three generations of PTH assays

KDIGO guidelines earlier recommended target iPTH levels of 2-9 times of the upper limit of normal for the given assay to noninvasively monitor bone status in dialysis patients. iPTH values above this target suggest high bone turnover bone disease with specificity of 86%, and values below the target values suggest low bone turnover with sensitivity of 66%. However, the latest update to the CKD-MBD guideline published by the KDIGO in 2017 suggest that in patients with CKD G3a–G5D, treatment for CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together and not absolute values of any of these parameters.[49]

Treatment options

A paradigm shift has occurred in the approach to the treatment of secondary and tertiary hyperparathyroidism with the understanding that the alterations in calcium and phosphate metabolism in CKD do not only cause renal osteodystrophy and bone abnormalities but also are linked to increased risk of cardiovascular disease and all-cause mortality potentially mediated through vascular calcification.[50]

The complex pathophysiology of secondary and tertiary hyperparathyroidism makes it necessary that their treatment should be multi-pronged. The three main targets are thus phosphate, 1,25 vitamin D and PTH.

Controlling Phosphate Levels

The management of hyperphosphatemia has formed the cornerstone of therapy for SHP for decades. Dietary phosphate restriction and treatment with oral phosphate binders can decrease PTH levels up to stages 3 and 4 CKD.[51] The reduction of protein intake (particularly protein of animal origin) has been the basis of dietary prescriptions in CKD. However, such a diet is difficult to maintain, and such dietary restrictions should be counter-balanced by the awareness that they may be associated with an increased risk of malnutrition in CKD patients. Nevertheless, all attempts should be made to have a diet that contains more vegetal than animal proteins and to avoid processed foods.

Most often, as CKD progresses and hyperphosphatemia ensues, dietary phosphate restriction alone is not helpful and phosphate binding medications are needed. An ever-increasing number of phosphate binders have been developed over the last few decades. They can be broadly grouped into calcium based and non–calcium-based agents. All these agents are more or less equally effective in the control of phosphate levels and SHP. Calcium-based phosphate binders such as calcium carbonate and calcium acetate are widely prescribed and very effectively lower Pi levels. However, their benefits must be weighed against possible adverse effects of hypercalcemia. KDOQI guidelines recommend that the total dose of elemental calcium provided through calcium-based phosphate binders should not exceed 1500 mg daily.[52]

One of the most commonly used non–calcium-based binders is Sevalamer; a phosphate binding resin. A meta-analysis of randomized controlled trials comparing calcium-based phosphate binders to non–calcium-based ones surmised that the use of calcium-based binders was associated with higher all-cause mortality compared to Sevalamer.[53] However, due to lack of placebo-controlled trials, the debate on whether calcium-based Pi binders are associated with higher risk for vascular calcifications and consequently for cardiovascular mortality continues.

Another non–calcium-based phosphate binder; Lanthanum carbonate has also been shown to control hyperphosphatemia. However, Lanthanum can be systemically absorbed and may accumulate in liver and bone. This limits its use as a first-line phosphate binder.

Enteral phosphate binders may lead to up-regulation of the intestinal sodium-phosphate NPT2b transporter thereby increasing active enteral phosphate absorption, off-setting some of their beneficial effects. Extended release Niacin, a NPT2b inhibitor has shown phosphate and FGF-23 lowering effects in adult CKD patients.[54] However, the recent CKD Optimal Management with Binders and Nicotinamide (COMBINE) study designed to assess whether the addition of NPT2b blockade to Lanthanum improves phosphate and FGF-23 levels showed disappointing results with no significant differences in any of the three active treatment groups (Nicotinamide plus Lanthanum Carbonate, Nicotinamide plus Placebo, or Lanthanum Carbonate plus Placebo) compared with the double placebo group though the findings could have been affected by the high non-compliance rates observed amongst the double-treatment group.[55] Tenapanor is a new agent that inhibits intestinal absorption of phosphate through the inhibition of intestinal sodium/hydrogen exchanger isoform 3 has recently been shown to effectively reduce phosphate in patients who are on maintenance dialysis.[56] It opens up a potential new therapeutic option in controlling of serum phosphate in patients with CKD.

Phosphate is also removed during dialysis. Hence it is vital that dialysis dose is adequate to optimize phosphate control. This can be achieved by adjusting dialysis time as well as blood flow settings during dialysis. It has been shown that patients who are on long/frequent dialysis have much better control of phosphate than their counterparts who are on conventional dialysis.[56]

Vitamin D analogues

Treatment with Vitamin D Receptor Activators (VDRAs) has long been a very important therapeutic strategy in the management of SHP. Calcitriol, the first synthetic VDRA to be developed decreases serum PTH levels[57,58] in CKD and also has been shown to reduce bone turnover and to thus ameliorate osteitis fibrosa in dialysis patients[59] though its effect on risk of fractures in CKD has not been adequately studied. The inhibitory effect on PTH synthesis is mediated through binding of calcitriol to its specific receptor (VDR) and subsequent regulation of gene transcription and inhibition of PTH mRNA synthesis. This is important to

know because in advanced SHP, with nodular hyperplasia of the parathyroid glands, there is decreased expression of CaSR and VDRs in the parathyroid gland[29,30], and in such a situation, VDRAs are not as effective in suppressing PTH secretion.[60] The clinical utility of Calcitriol is limited by its potential to cause hypecalcemia. The newer selective VDRAs such as paricalcitol (19-nor-1,25-dihydroxyvitamin D2) and maxacalcitol (22-oxa-1,25-dihydroxyvitamin D3) may be preferable in this regard because they have more modest effects on serum calcium levels though it has to be noted that these agents can also cause hypercalcemia.

Although it has long been known that vitamin D deficiency is common in CKD patients, the common belief has been that the need for its correction is not as stringent in this clinical setting provided that active vitamin D is administered. However, the administration of native vitamin D may have other pleuripotent benefits and it has also been demonstrated that use of native vitamin D esters are effective in lowering PTH levels at least in the early stages of SHP.[61]

Calcimimetics

The introduction of calcimimetics, agents that allosterically activate the calcium sensing receptor, has significantly mitigated the need for high doses of activated vitamin D and the risk of hypercalcemia in SHP. These agents "mimic" calcium and increase the sensitivity of calcium sensing receptors on the parathyroid gland. Currently, the only oral calcimimetic approved by the FDA is Cinacalcet. Cinacalcet effectively reduces PTH levels and serum calcium levels in patients with SHP.[62] Notably, cinacalcet is effective even in patients with marked parathyroid hyperplasia[63] thus making it an acceptable alternative to parathyroidectomy for treatment of severe SHP. Cinacalcet may cause gastrointestinal adverse effects such as nausea and vomiting. The introduction of a new intravenous calcimimetic, Etelcalcetide offers a therapeutic alternative to oral cinacalcet.[64] Etelcalcetide has a longer half-life than cinacalcet and can be administered intravenously every other day at the end of dialysis treatment thus overcoming the problem of compliance with a daily oral regimen. Etelcalcetide has been shown to markedly decrease PTH levels in patients on hemodialysis with moderate to severe SHP and may be superior to Cinacalcet in this regard[65] though further studies are needed to assess clinical outcomes as well as long-term efficacy and safety of this agent.

The effects of Cinacalcet on bone turnover and bone histology in patients with CKD and evidence of high-turnover bone disease have been studied in the Bone Histomorphometry Assessment for dialysis patients with Secondary Hyperparathyroidism of End-Stage Renal Disease (BONAFIDE) study.[66] This study demonstrated that long-term treatment with cinacalcet lowers biochemical markers of high bone-turnover and improves bone histology in this setting. In the Evaluation of Cinacalcet Hydrochloride therapy to Lower Cardiovascular Events (EVOLVE) trial, a randomized controlled trial to assess the effects of cinacalcet on clinical outcomes, though no significant effect of cinacalcet in the primary intention to treat analysis was seen, a significant reduction in the risk of fracture in the cinacalcet group was found when differences in baseline characteristics, multiple fractures and/or events prompting discontinuation of study drug were taken into account.[67] The results of the EVOLVE trial also suggested a beneficial effect of Cinacalcet with regard to reduction in the risk of death or cardiovascular outcomes though it has to be noted that this again was not in the primary unadjusted intention to treat analysis but in the log-censoring analysis.[68]

Parathyroidectomy

Despite the availability of newer vitamin D analogues and calcimimetics, parathyroidectomy continues to be a necessity in certain patient groups. It is estimated that parathyroidectomy is required in about 15% of patients after 10 years and in 38% of patients after 20 years of ongoing dialysis therapy.[69] Successful surgical treatment results in a dramatic reduction in PTH levels and improvement of clinical symptoms such as bone pain and itching. Parathyroidectomy is also associated with better patient survival[70-72] and reduced risk of fractures[73] in patients with severe SHP.

A description of the surgical techniques for parathyroidectomy is beyond the scope of this article. The choice of surgical technique viz subtotal parathyroidectomy versus total parathyroidectomy with auto transplantation ultimately depends on operator experience and expertise and must be individualized to the patient. However, parathyroidectomy is not without its risk. The most commonly seen is the phenomenon of Hungry Bone Syndrome[74] characterized by severe hypocalcemia post parathyroidectomy. The abrupt withdrawal of very high and sustained levels of PTH following parathyroidectomy, turns off osteoclast activity and bone resorption in the remodeling space. However, osteoblast activity and new bone formation continues, which leads to the influx of calcium, phosphate and magnesium into bone resulting in their abrupt drops in the serum. This condition remains poorly defined and the prevalence of this condition has been reported to range from 8% to 87% following parathyroidectomy for SHP.[75] The other concern is the occurrence of adynamic bone disease and hypoparathyroidism post parathyroidectomy. Hypoparathyroidism typically is reported following surgery for PHPT and there is no study that reports the incidence or prevalence of this condition in patients who undergo parathyroidectomy for SHP. Low turnover bone disease, however, has been reported to occur post parathyroidectomy and has been associated with worsening of vascular calcification in hemodialysis patients.[76-78]

Chemical ablation of parathyroid gland

Percutaneous fine needle ethanol injection of parathyroid gland was first reported in 1985 in 12 patients with SHP.[79] In 2003, the Japanese Society of Parathyroid Intervention published its guideline for selective percutaneous ethanol injection therapy of the parathyroid glands in chronic dialysis patients in which they recommended that enlarged parathyroid glands

with nodular hyperplasia could be "selectively" destroyed by ethanol injection, and other glands with diffuse hyperplasia could be then managed by medical therapy.[80]

Percutaneous injection using the Vitamin D analogue-Calcitriol instead of alcohol has also been described.[81] The rationale behind this approach is to introduce high level of vitamin D around the parathyroid gland without the systemic complications that could potentially be caused by its systemic administration.

These local approaches could be considered in patients who refuse or are not candidates for surgery although long-term control of SHP is unlikely to be obtained.

Persistent hyperparathyroidism after kidney transplantation

Persistent hyperparathyroidism even after renal transplantation is most likely to be present in patients with advanced SHP with nodular hyperplasia of the parathyroid glands before transplant. It is the most common cause of hypercalcemia[82] in renal transplant patients and may result in poor graft outcomes and progression of vascular calcification.[83] Surgical parathyroidectomy should be considered in kidney transplant patients with persistent hyperparathyroidism especially when it is associated with severe hypercalcemia. Cinacalcet appears to be a promising therapeutic option for patients with persistent hypercalcemia post transplantation at least as a bridging agent before parathyroidectomy.[84-86]

Conclusion

Our knowledge of the pathophysiology of secondary and tertiary hyperparathyroidism has vastly improved during the past few years. They may be caused by various conditions, however, that associated with CKD has been the one most studied and yet remains incompletely defined. The clinical consequences of these disorders of the parathyroid gland are not limited to the musculo-skeletal system but are multifold and systemic. It is however difficult to define clearly whether there is a causal relationship between the elevated levels of PTH seen in these disorders and the protean clinical manifestations or whether they simply are associations in a complex clinical setting. The number of available therapeutic options for the management of secondary and tertiary hyperparathyroidism has increased significantly and control of PTH, phosphate and calcium levels can be successfully achieved in most cases with these medications. However convincing benefits on major clinical outcomes such as prevention of fractures, cardiovascular events or survival have not been demonstrated so far and a significant percentage of patients still need parathyroidectomy – the approach to which should be undertaken on an individualized basis.

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Conflicts of interest

There are no conflicts of interest.

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