Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 16, no. 1, 64–68, 2013

1094-6950/16:64–68/$36.00
http://dx.doi.org/10.1016/j.jocd.2012.11.012

Original Article

Secondary and Tertiary Hyperparathyroidism

Sophie A. Jamal[*,1] *and Paul D. Miller*[2]

[1]*University of Toronto, Women's College Research Institute, Toronto, Ontario, Canada; and* [2]*Colorado Center for Bone Research, Lakewood, CO, USA*

Abstract

We reviewed the etiology and management of secondary and tertiary hyperparathyroidism. Secondary hyperparathyroidism is characterized by an increase in parathyroid hormone (PTH) that is appropriate and in response to a stimulus, most commonly low serum calcium. In secondary hyperparathyroidism, the serum calcium is normal and the PTH level is elevated. Tertiary hyperparathyroidism is characterized by excessive secretion of PTH after longstanding secondary hyperparathyroidism, in which hypercalcemia has ensued. Tertiary hyperparathyroidism typically occurs in men and women with chronic kidney disease usually after kidney transplant. The etiology and treatment of secondary hyperparathyroidism is relatively straightforward whereas data on the management of tertiary hyperparathyroidism is limited to a few small trials with short follow-up.

Key Words: Chronic kidney disease; hyperparathyroidism; serum calcium.

Definition of Hyperparathyroidism

Most of the articles in this issue of *Journal of Clinical Densitometry* deals with the many and varied manifestations of primary hyperparathyroidism (PHPT). It is important to distinguish between a primary disorder of the parathyroid gland(s), in which there is incompletely regulated, excessive secretion of parathyroid hormone (PTH) as in the cases of PHPT, and physiological situations in which the parathyroid glands have responded to a stimulus that appropriately leads to increased PTH secretion. These forms of hyperparathyroidism are known as secondary hyperparathyroidism. By definition, in secondary hyperparathyroidism, the serum calcium concentration is normal but the PTH level is elevated. The major stimulus to increased PTH secretion is in response to a reduction in the serum calcium concentration. For example, any malabsorption syndrome in which calcium absorption is impaired can be associated with an increase in PTH secretion. Renal insufficiency defined by a creatinine clearance lower than 60 mL/min is often associated with an increase in PTH. Vitamin D deficiency, as defined by a low 25-hydroxyvitamin D level, can be associated with an increase in PTH. The definition of vitamin D is somewhat controversial with some experts considering a level lower than 20 ng/mL (50 nmol/L) as the threshold, whereas others feel that a level lower than 30 ng/mL (75 nmol/L) is the threshold of vitamin D adequacy. For the purposes of defining secondary hyperparathyroidism, however, it is important to consider a level of 25-hydroxyvitamin D that is clearly sufficient, namely higher than 30 ng/mL (> 75 nmol/L). Drugs such as lithium and thiazide diuretics can be associated with an increase in PTH levels.

This article focuses mainly on tertiary hyperparathyroidism, characterized by excessive secretion of PTH after long-standing secondary hyperparathyroidism in which hypercalcemia has ensued. It is important to be clear on terminology. Although both secondary and tertiary hyperparathyroidism result from a chronic stimulus to PTH secretion, the serum calcium is always normal in the former, whereas it is always elevated in the latter. Tertiary hyperparathyroidism can be the end result of long-standing secondary hyperparathyroidism in which the stimulated parathyroid glands are no longer in a reactive mode but have assumed a quasi-autonomous function, not too dissimilar from PHPT. The distinction between PHPT and tertiary hyperparathyroidism is usually self-evident in that a clearly

Accepted 11/18/12.
*Address correspondence to: Sophie A. Jamal, MD, PhD, FRCPC, University of Toronto, Women's College Research Institute, 760 Bay Street, 7th Floor, Toronto, ON M5G 1N8 Canada. E-mail: sophie.jamal@utoronto.ca

definable disorder is present, such as long-standing malabsorption or renal failure.

Etiology of Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is characterized by the semiautonomous hypersecretion of PTH leading to hypercalcemia. The cellular etiology of tertiary hyperparathyroidism is unknown but is postulated to be owing to a monoclonal expansion of a clone of parathyroid cells, which have acquired an altered set point of their calcium-sensing receptor (CASR) so that PTH is secreted despite high serum calcium levels. Tertiary hyperparathyroidism is most commonly observed in patients with long-standing chronic kidney disease (CKD) and often after renal transplantation. To understand why tertiary hyperparathyroidism occurs in men and women with CKD, posttransplant, one must first consider why patients with CKD develop secondary hyperparathyroidism.

Long-standing CKD is associated with several metabolic disturbances that lead to increased secretion of PTH, including hyperphosphatemia, calcitriol deficiency, and hypocalcemia (Table 1 and Fig. 1). Hyperphosphatemia has a direct stimulatory effect on the parathyroid gland cell resulting in nodular hyperplasia and increased PTH secretion *(1,2)*. Hyperphosphatemia also increases PTH indirectly: the stimulus to hyperphosphatemia caused by a reduction in filtered phosphate is reversed through PTH and fibroblast growth factor (FGF)-23–mediated reductions in tubular epithelial phosphate transport *(3)*. The increase in phosphate excretion per remaining nephron restores phosphate homeostasis at the cost of higher PTH and FGF-23 levels and maintains normal phosphate excretion. In short time, FGF-23 is able to reduce PTH secretion, but in CKD there may be decreased parathyroid cell membrane expression of FGF-23 receptors and its coreceptor, Klotho, so that even high levels of FGF-23 cannot inhibit PTH production *(4)*.

As CKD advances, the decreased nephron mass results in a decrease in proximal tubular 1-α-hydroxylase activity and calcitriol production *(5)*. The decrease in calcitriol decreases intestinal calcium absorption, which leads to hypocalcemia stimulating PTH secretion (described in more detail below). With even more advanced renal failure, there is a decrease in tissue levels of vitamin D receptors (VDRs), particularly in the parathyroid gland cells; 1 role of the VDR is to suppress the expression of prepro-PTH mRNA *(6,7)*. Thus, the low levels of calcitriol together with low levels of VDR increase the synthesis and secretion of PTH.

Low blood levels of ionized calcium stimulate PTH secretion through activation of the CASR. In a short time, stimulation of PTH secretion by hypocalcemia is caused by exocytosis of PTH packaged in granules. With longer-term hypocalcemia, there is an increase in the number of cells that secrete PTH *(8)*.

The size of the parathyroid glands progressively increases as CKD worsens, and gland size is positively correlated with serum PTH levels. The increase in gland size is primarily because of diffuse cellular hyperplasia, but there is also monoclonal chief cell growth, resulting in the formation of nodules. Nodular hyperplastic glands have less VDRs and CASRs compared with diffusely hyperplastic glands, a fact that further exacerbates parathyroid gland resistance to calcitriol and calcium. Because the parathyroid glands are autonomously functioning, in some patients, PTH levels remain persistently high despite serum calcium levels that are within the reference range or even above normal after a renal transplant and so called tertiary hyperparathyroidism. Posttransplantation that usually results in a return to normal biology of phosphorus homeostasis and an increase in 1,25-dihydroxyvitamin D production may not be sufficient to reduce PTH or serum calcium levels if the tissue mass is great enough to act semiautonomously.

Other rare causes of tertiary hyperparathyroidism include X-linked hypophosphatemic rickets, adult-onset (autosomal dominant) hypophosphatemic rickets, and oncogenic osteomalacia. These diseases are chronic and treated with high-dose oral phosphate, which increases plasma phosphate; the increase in phosphate transiently decreases ionized calcium and results in a decreased production of 1,25-dihydroxyvitamin D. The aberrations in mineral metabolism lead to parathyroid stimulation and secretion of PTH, which, over time, can result in autonomous function of the parathyroid glands that may be associated with either frank hypercalcemia or serum calcium, which is in the normal range despite a high serum PTH level *(9–14)*. In all 3 diseases, there is an increase in FGF-23, which also contributes to the suppression of 1,25-dihydroxyvitamin D production. To repair the mineralization defect in these diseases, replacement of 1,25-dihydroxyvitamin D in addition to phosphate is required.

Table 1
Factors Contributing to Secondary Hyperparathyroidism in Renal Disease

	Mechanism	
Factors	Direct	Indirect
Hyperphosphatemia	Stimulates the parathyroid glands	PTH-mediated reduction in tubular phosphate transport
Calcitriol	Decreased VDR receptors increase in secretion of prepro-PTH mRNA	Hypocalcemia

Abbr: PTH, parathyroid hormone; VDR, vitamin D receptor.

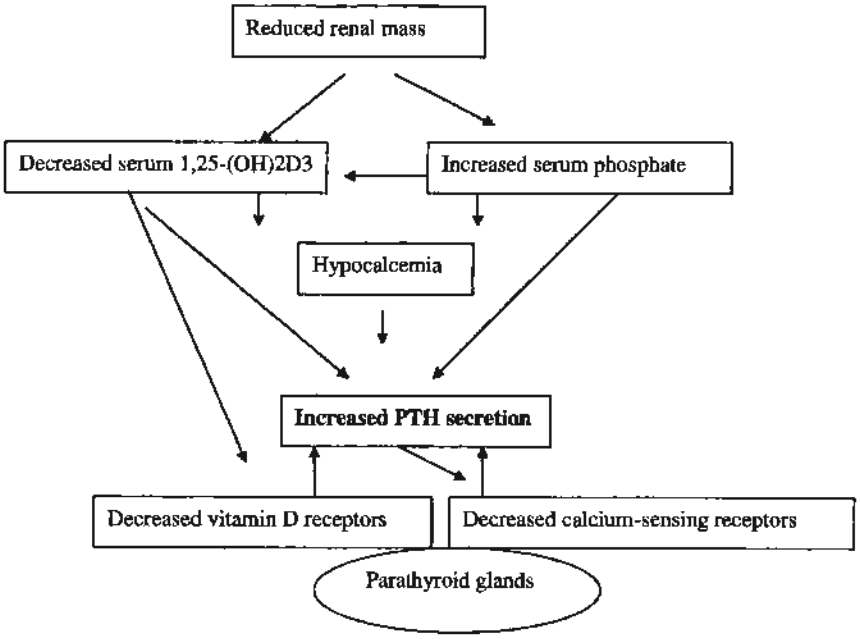

Fig. 1. Pathophysiology of secondary hyperparathyroidism. 1,25-(OH)2D3, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.

Clinical Presentation of Tertiary Hyperparathyroidism

Most commonly, these patients are identified by the presence of persistent hyperparathyroidism and hypercalcemia after renal transplantation. Although a successful renal transplant will reverse most of the bone and mineral abnormalities in most patients, persistently elevated PTH with or without increases in serum calcium is sometimes seen. Data that report on the prevalence of these mineral abnormalities are scarce. A recent, and the largest to date, retrospective observational study reported that among 607 patients with successful renal transplants, 108 (52%) had an elevated PTH 1-yr after transplantation, and 47 (8%) had an increase in both PTH and serum calcium levels *(15)*.

Although tertiary hyperparathyroidism characterized by the combination of simultaneous hypercalcemia with elevated PTH levels is most often seen in severe CKD patients after renal transplantation, it is important to exclude other either pre- or coexisting conditions that might have this same biochemical combination. These include a preexisting and uncorrected PHPT, continual prescribing of drugs designed to suppress PTH during severe CKD that might also cause hypercalcemia (eg, calcitriol), or continual use of drugs indicated for psychiatric disorders (eg, lithium).

Symptoms and signs of tertiary hyperparathyroidism may be similar to PHPT attributed to the level of PTH or level of hypercalcemia, and can include bone pain, decreased bone mineral density (BMD), fractures, pruritus, nephrolithiasis, peptic ulcer disease, pancreatitis, soft tissue or vascular calcifications, muscle weakness, mental status changes, and impaired graft function *(16)*.

Treatment

There are neither evidence-based guidelines for the treatment of tertiary hyperparathyroidism nor are there large trials comparing interventions. The main indication for treatment is persistent hypercalcemia and/or an increased PTH, and the primary treatment is surgery. The purpose of surgical treatment is to reduce the parathyroid mass and cell number and, thus, normalize the serum calcium concentration. Although there are no universally accepted clinical guidelines as to when to intervene, the most obvious indication is long-term sustained hypercalcemia (> 11.0 mg/dL), similar to 1 of the indications established by the National Institutes of Health for intervention in asymptomatic PHPT *(17)*. Although there is no specific cutoff level of serum PTH that dictates intervention, sustained PTH levels (a trend rather than a single measurement), 2–9 times above the upper limit of normal, even with normocalcemia, should lead to consideration of parathyroidectomy. This last PTH cutpoint is also not dissimilar from the Kidney Disease Improving Global Outcome recommendation for management of secondary hyperparathyroidism in severe CKD cases *(18)*. It is important to stress that mild hypercalcemia and/or hyperparathyroidism are common during the first 12 mo after renal transplantation, and decisions regarding management should be delayed for 12 mo allowing the return of phosphorus, calcium, and vitamin D homeostasis to normal unless a more severe "hypercalcemic crisis" dictates earlier intervention. In addition, because severe hypophosphatemia can be observed early after renal transplantation, careful replacement and monitoring of the serum phosphorus may be indicated in early hypercalcemia after transplantation *(19,20)*.

Surgical strategies can be broadly divided into subtotal or total parathyroidectomy with or without autotransplantation *(21)*. Decisions about which approach is used are typically determined by the surgeon on a case-by-case basis; there are limited long-term follow-up data and even fewer data concerning which strategy if any is superior. One recent trial compared outcomes in 14 of 488 renal transplant patients who developed tertiary hyperparathyroidism by surgical procedure, specifically total (n = 7) vs subtotal parathyroidectomy (n = 7) followed for 6-mo postoperatively *(22)*. The authors reported no difference in operative time, duration of hospital stay, weight of the gland, or differences in laboratory parameters other than calcium and phosphate. However, those undergoing total parathyroidectomy had lower serum calcium and higher serum phosphate levels. This led the authors to conclude that subtotal parathyroidectomy is the preferred surgical treatment as it reduces the risk of hypocalcemia. In contrast, a retrospective chart review reported on 26 subjects with renal transplants who underwent total parathyroidectomy without autotransplantation; 5-yr follow-up was available for all subjects and 9-yr data for 20 subjects. After surgery, all patients received 1-α-calcidiol. The authors reported that at both 5 and 9 yr, serum calcium and serum PTH were normal and concluded that total parathyroidectomy without autotransplantation appears to be protective against persistent and recurrent diseases *(23)*.

Another potential treatment option is calcimimetics, such as cinacalcet. Calcimimetics inhibit PTH secretion by modulating the CASR in the parathyroid gland. Although calcimimetics are not approved for treating tertiary hyperparathyroidism, there have been a few small (total subjects: 37 patients), open-label trials of short duration (10–26 wk) *(24–26)*. All of these trials reported that serum calcium decreased and in most cases normalized, and 2 of the 3 studies reported a significant decrease in serum PTH *(24,25)*. There were no changes in renal function and no adverse events. A recent study reported on effects of stopping cinacalcet after 12 mo of treatment in 10 patients *(27)*. The follow-up in this study was 3 mo and was limited to measurement of calcium, phosphate, PTH, creatinine, and cystatin C. The authors reported that by 3 mo of discontinuation, serum calcium increased, but it remained in normal range in 8 of 10 subjects, with no change in serum PTH level. The authors concluded that it might be reasonable to consider a trial of cinacalcet cessation in patients taking cinacalcet for the treatment of tertiary hyperparathyroidism. Clearly, larger, prospective, randomized controlled trials are needed.

In conclusion, the diagnostic "label" of tertiary hyperparathyroidism (the combination of sustained elevated serum PTH and sustained hypercalcemia) is given by International Classification of Diseases code when it is not because of PHPT, *familial hypocalciuric hypercalcemia*, or conditions (usually iatrogenic) that can lead to this combination of biochemical abnormalities (eg, lithium) in patients without CKD, or calcitriol use in patients with CKD and secondary hyperparathyroidism. Other causes of secondary hyperparathyroidism are usually accompanied by hypocalcemia, which is the reason why these latter patients have a secondary etiology for a normal biological response to explain the increased PTH (vitamin D insufficiency, malabsorption, or CKD).

Tertiary hyperparathyroidism is most often seen after renal transplantation where the chronic stimulants for the increased parathyroid cell mass and/or function are partially corrected (hyperphosphatemia and reduced 1,25-dihydroxyvitamin D production), but the PTH level is not sufficiently suppressed so that PTH levels may remain elevated. Although the PTH levels per se may come down over time, and not be of clinical concern unless they are above levels considered potentially "unacceptable" by specific guidelines, the major indication for intervention to reduce the PTH level (surgically or medically) is sustained hypercalcemia. Hypercalcemia above 11.0 mg/dL that is consistent and sustained may lead to unacceptable adverse consequences (vascular calcification or reduction in renal graft function) and is a widely accepted indication for intervention. Other management strategies for these patients include monitoring serum phosphorus, renal function, and skeletal health by serial BMD and measurements of bone-specific alkaline phosphatase. Although baseline BMD, especially by dual-energy X-ray absorptiometry (DXA), is a poor predictor for fractures in these severe CKD patients, changes in BMD by DXA may provide valuable information when performed and interpreted correctly *(28,29)*. Although we need more longitudinal data to better understand the natural biology and management of this growing population of posttransplant renal patients, we do have the tools to measure the changes in PTH, calcium, phosphorus, and bone to make adequate clinical decisions concerning management based on growing data at this time.

References

1. Moallem E, Kilav R, Silver J, Naveh-Many T. 1998 RNA-protein binding and post-transcriptional regulation of parathyroid hormone gene expression by calcium and phnsphate. J Biol Chem 273:5253–5259.
2. Naveh-Many T, Rahamimov R, Livni N, Silver J. 1995 Parathyroid cell proliferation in normal and chronic renal failure rats. The effects of calcium, phosphate, and vitamin D. J Clin Invest 96:1786–1793.
3. Slatopolsky E, Robson AM, Elkan I, Bricker NS. 1968 Control of phosphate excretion in uremic man. J Clin Invest 47:1865–1874.
4. Jonsson KB, Zahradnik R, Larsson T, et al. 2003 Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med 348:1656–1663.
5. Goodman WG, Quarles LD. 2008 Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. Kidney Int 74:276–288.
6. Naveh-Many T, Marx R, Keshet E, et al. 1990 Regulation of 1,25-dihydroxyvitamin D3 receptor gene expression by 1,25-dihydroxyvitamin D3 in the parathyroid in vivo. J Clin Invest 86:1968–1975.
7. Silver J, Russell J, Sherwood LM. 1985 Regulation by vitamin D metabolites of messenger ribonucleic acid for preproparathyroid hormone in isolated bovine parathyroid cells. Proc Natl Acad Sci U S A 82:4270–4273.
8. Brown EM, Hebert SC. 1995 A cloned Ca(2+)-sensing receptor: a mediator of direct effects of extracellular Ca2+ on renal function? J Am Soc Nephrol 6:1530–1540.

9. Sato K, Obara T, Yamazaki K, et al. 2001 Somatic mutations of the MEN1 gene and microsatellite instability in a case of tertiary hyperparathyroidism occurring during high phosphate therapy for acquired, hypophosphatemic osteomalacia. J Clin Endocrinol Metab 86:5564–5571.
10. Rivkees SA, el-Hajj-Fuleihan G, Brown EM, Crawford JD. 1992 Tertiary hyperparathyroidism during high phosphate therapy of familial hypophosphatemic rickets. J Clin Endocrinol Metab 75:1514–1518.
11. Knudtzon J, Halse J, Monn E, et al. 1995 Autonomous hyperparathyroidism in X-linked hypophosphataemia. Clin Endocrinol 42:199–203.
12. Makitie O, Kooh SW, Sochett E. 2003 Prolonged high-dose phosphate treatment: a risk factor for tertiary hyperparathyroidism in X-linked hypophosphatemic rickets. Clin Endocrinol 58: 163–168.
13. Shimada T, Hasegawa H, Yamazaki Y, et al. 2004 FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 19:429–435.
14. Huang QL, Feig DS, Blackstein ME. 2000 Development of tertiary hyperparathyroidism after phosphate supplementation in oncogenic osteomalacia. J Endocrinol Invest 23: 263–267.
15. Bleskestad IH, Bergrem H, Leivestad T, Goransson LG. 2011 Intact parathyroid hormone levels in renal transplant patients with normal transplant function. Clin Transplant 25:E566–E570.
16. Gilat H, Feinmesser R, Vinkler Y, et al. 2007 Clinical and operative management of persistent hyperparathyroidism after renal transplantation: a single-center experience. Head Neck 29: 996–1001.
17. Bilezikian JP, Potts JT Jr, Fuleihan Gel H, et al. 2002 Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Bone Miner Res 17(Suppl 2):N2–11.
18. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). 2009 Kidney Int Suppl: S1–S130.
19. Huang M, Sprague SM. 2009 Bone disease in kidney transplant patients. Semin Nephrol 29:166–173.
20. Mainra R, Elder G. 2009 Review article: Managing bone complications after kidney transplantation. Nephrology (Carlton) 14:437–442.
21. Schlosser K, Endres N, Celik I, et al. 2007 Surgical treatment of tertiary hyperparathyroidism: the choice of procedure matters! World J Surg 31:1947–1953.
22. Hsieh TM, Sun CK, Chen YT, Chou FF. 2012 Total parathyroidectomy versus subtotal parathyroidectomy in the treatment of tertiary hyperparathyroidism. Am Surg 78:600–606.
23. Sadideen HM, Taylor JD, Goldsmith DJ. 2012 Total parathyroidectomy without autotransplantation after renal transplantation for tertiary hyperparathyroidism: long-term follow-up. Int Urol Nephrol 44:275–281.
24. Serra AL, Schwarz AA, Wick FH, et al. 2005 Successful treatment of hypercalcemia with cinacalcet in renal transplant recipients with persistent hyperparathyroidism. Nephrol Dial Transplant 20:1315–1319.
25. Serra AL, Savoca R, Huber AR, et al. 2007 Effective control of persistent hyperparathyroidism with cinacalcet in renal allograft recipients. Nephrol Dial Transplant 22:577–583.
26. Kruse AE, Eisenberger U, Frey FJ, Mohaupt MG. 2005 The calcimimetic cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism. Nephrol Dial Transplant 20:1311–1314.
27. Kruse AE, Eisenberger U, Frey FJ, Mohaupt MG. 2007 Effect of cinacalcet cessation in renal transplant recipients with persistent hyperparathyroidism. Nephrol Dial Transplant 22:2362–2365.
28. Jamal SA, West SL, Miller PD. 2012 Bone and kidney disease: diagnostic and therapeutic implications. Curr Rheumatol Rep 14:217–223.
29. West SL, Jamal SA. 2012 Determination of bone architecture and strength in men and women with stage 5 chronic kidney disease. Semin Dial 25:397–402.