Understanding Hyperparathyroidism in Renal Disease

Rosemary Nwoko, MD, and Kara Chenitz, MD

The parathyroid glands are four pea-sized glands located on the four corners of the thyroid gland. They secrete parathyroid hormone (PTH), which maintains calcium and phosphorus homeostasis.[8] PTH regulates calcium such that when serum levels of calcium fall too low, it increases the serum calcium level by stimulating more calcium release from the bones, increasing intestinal absorption of calcium and decreasing calcium excretion into the urine.[9] When the serum calcium normalizes, the parathyroid gland shuts off the production of PTH. An excess of PTH in the system throws off the calcium-phosphorus homeostatic balance, resulting in various symptoms and clinical effects.

Hyperparathyroidism can be of two types: primary and secondary.[8] The former is commonly due to an adenoma or hyperplasia of one or more of the four glands. In rare cases, primary hyperparathyroidism can be secondary to a malignancy in the glands. Secondary hyperparathyroidism occurs when elevated PTH levels are caused by pre-existing medical conditions such as calcium malabsorption syndromes, disorders of vitamin D and phosphate metabolism, dietary calcium deficiency or any other pre-existing condition that causes low serum calcium levels with a resultant compensatory increase in PTH levels. Chronic renal failure is the most common cause of secondary hyperparathyroidism and will be the focus of this review. CKD patients have high phosphate and low calcium levels causing hypocalcemia and a resultant stimulation of the parathyroid glands.[9]

Patients with hyperparathyroidism develop a wide array of symptoms and complications, although some patients may be asymptomatic initially. This includes but is not limited to myopathy, fatigue, pruritis, abdominal pain, renal calculi, confusion, memory problems, osteoporosis, and increased thirst and urination (due to the increased excretion of calcium into the urine causing an osmotic effect).[11] With continued elevation of PTH and therefore serum calcium levels, conjunctival, corneal, vascular and cutaneous calcification can occur with severe consequences.[1,8] Vascular calcification is the most dreaded complication of hyperparathyroidism because it results in plaque accumulation that increases the risk of cardiovascular death. Patients can develop calcium calcification in the myocardium, coronary arteries, and cardiac valves. They are also at risk for palpitations, hypertension, and arrhythmias such as atrial fibrillation.[1,11] Indeed, the most common cause of death in end stage renal disease (ESRD) patients is cardiovascular disease.[1] As another example of a serious complication, cutaneous calcification can result in ulceration and gangrene.[1] Hyperparathyroid induced bone disease, or osteitis fibrosa cystica, which is due to increased osteoclast and osteoblast activity, also occurs commonly with longstanding hyperparathyroidism.

Medical management of hyperparathyroidism includes calcium supplements, vitamin D analogs, phosphate binders and/or calcimimetics that have various mechanisms of action to suppress the high PTH level. Calcium stimulates the G-protein linked calcium sensing receptor (CaSR), inhibiting the release of PTH at secondary sites (e.g., c cells of thyroid gland, kidney cells, osteoblasts, GI mucosa, and hematopoietic cells in the bone marrow).[10] Vitamin D acts directly on parathyroid cell vitamin D receptors to inhibit PTH release and phosphate binders work by binding phosphate in the intestinal lumen. Calcimimetics, such as cinacalcet, increase the CaSR's sensitivity to serum calcium.[4] Calcimimetics are especially beneficial because they stimulate the calcium receptors without additionally increasing calcium, unlike vitamin D analogs. Also this class of drugs is particularly useful in those patients with ESRD who have nodular hyperplasia of the parathyroid gland which causes decreased expression of extracellular CaSR and even greater reduction in vitamin D receptor density. This leads to decreased efficacy of calcium and vitamin D analogs. When medical therapy fails, surgical removal by subtotal parathyroidectomy is the next available option.

At this point, there is no official standard of care regarding the absolute indications for parathyroidectomy in hyperparathyroidism generally or with respect to patients with ESRD.[2] Many of the symptoms discussed earlier can be present in dialysis patients who do not have markedly elevated levels of PTH, who therefore would not benefit from parathyroidectomy. As mentioned above, a nodular, hyperplastic parathyroid gland provides fewer options for medical treatment, so in these cases surgery may be indicated. In renal transplant recipients, most hyperparathyroidism improves post transplantation but when it does not, the persistent hyperparathyroidism may adversely affect renal function, leading to consideration of surgical intervention. Studies have shown that parathyroidectomy has beneficial effects on humoral immunological markers. The effects are thought to be due to the marked PTH reduction and partly improved nutritional state after surgery.[2] Though this may be an attractive postoperative benefit, no studies have suggested that this is an indication for surgery. Unfortunately, post-transplant parathyroidectomy itself has been shown to be associated with abrupt decompensation of renal allografts,[6] so if patients have persistent hyperparathyroidism despite renal transplantation and medical therapy, they are left with grim options; they can either continue medical therapy and risk calciphylaxis, or get surgery and risk graft failure. Overall, since most abnormal parathyroid function normalizes after transplantation, there is little evidence to suggest a prophylactic parathyroidectomy is efficacious in patients on the renal transplant list. For now, nephrologists must rely on clinical instinct for the management of hyperparathyroidism, while research is underway delineating particular standards of care in this area.

References

1. Behdad, A. Vascular calcification in chronic kidney disease. In: UpToDate, Goldfarb, S (M.D.), UpToDate, Waltham, MA, 2008.
2. Berkoben, M, Cronin, RE, Quarles, LD. Indication for parathyroidectomy in end-stage renal disease. UpToDate. Ed. Schwab, SJ. Waltham, MA: 2008.
3. Block, GA, Raggi, P, Bellasi, A, *et al.* Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney International. 2007; 71:438.
4. Block, GA, Martin, KJ, de Francisco, ALM, *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. New England Journal of Medicine. 2004; 350:1516.
5. Katoh, N, Nakayama, M, Shigematsu, T, *et al.* Presence of sonographically detectable parathyroid glands can predict resistance to oral pulsed-dose calcitriol treatment of secondary hyperparathyroidism. American Journal of Kidney Diseases. 2000; 35:465.
6. Rostaing, L, Moreau-Gaudry, X, Baron, E, *et al.* Changes in blood pressure and renal function following subtotal parathyroidectomy in renal transplant patients presenting with persistent hypercalcemic hyperparathyroidism. Clinical Nephrology 1997; 47:248.
7. Yasunaga, C, Nakamoto, M, Matsuo, K, *et al.* Effects of a parathyroidectomy on the immune system and nutritional condition in chronic dialysis patients with secondary hyperparathyroidism. American Journal of Surgery. 1999; 178:332.
8. The Merck Manual 17th edition. Ed. Mark H. Beers, Robert Berkow . Whitehouse Station, NJ: Merck Research Labs, 1999. 1845-48.
9. Slatopolsky, E. The regulation of parathyroid hormone in health and in chronic renal failure. Journal of Bone and mineral metabolism. 1991; 9:39-44.
10. Bowen, R. "The Extracellular Calcium-Sensing Receptor." September 28, 2003. www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/casensor.html
11. Norman, J, Politz D. "Symptoms of Parathyroid Disease." January 2, 2009. www.parathyroid.com/parathyroid-symptoms.htm

Photograph courtesy of Anastasia Shnitser, MD