# Chapter 13
# Medical Management of Primary Hyperparathyroidism

**Ann E. Kearns**

## Case Presentation

A 53-year-old woman is seen for persistent primary hyperparathyroidism (PHPT). She has a complex past history of PHPT. She was originally found to be hypercalcemic at age 39 on routine blood tests performed prior to initiating medication for psoriasis. Testing confirmed the presence of PHPT: calcium 14.1 mg/dL (8.9–10.2 mg/dL), parathyroid hormone (PTH) 30 pg/mL (1.0–5.2 pg/mL), and 24 h urine calcium 321 mg/24 h. She had no family history of hypercalcemia or endocrine tumors. She had no personal history of kidney stones, head and neck irradiation, lithium use, or fractures. She underwent her first neck exploration with removal of a right inferior parathyroid adenoma weighing 1.56 g. Her calcium never completely normalized. She subsequently has undergone a total of five neck

A.E. Kearns, MD, PhD
Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo College of Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: kearns.ann@mayo.edu

A.E. Kearns, R.A. Wermers (eds.), *Hyperparathyroidism: A Clinical Casebook*, DOI 10.1007/978-3-319-25880-5_13,

explorations without complete resolution of hypercalcemia. Her bone density is normal in the lumbar spine and hips and osteopenic at the one-third radius with a T-score of −1.6. She has no recurrent laryngeal nerve damage. Her current laboratories show calcium 11.9 mg/dL (8.9–10.2 mg/dL) and PTH 215 pg/mL (10–65 pg/mL). She has symptoms of fatigue and depression. Her only other medical problem is psoriasis. Parathyroid scan, neck ultrasound, and a four-dimensional computed tomography (4D CT) scan do not identify abnormal parathyroid gland.

## Assessment and Diagnosis

Surgery is the treatment of choice for PHPT and is highly curative of the disorder. However, in the reoperative case for persistent (as this patient has) or recurrent PHPT, the cure rate is dramatically reduced with increasing number of operations [1]. Medical management of patients with PHPT is considered when surgery is not recommended due to comorbid medical conditions, unsuccessful or complicated prior surgery, or based on patient choice. Patients not undergoing surgery should be assessed for current complications of PHPT with appropriate imaging (e.g., bone density testing, kidney imaging for nephrolithiasis) and blood tests to assess calcium and kidney function.

A recent consensus statement on medical management of PHPT recommended that patients with PHPT be advised to consume the same amount of calcium as the general population and vitamin D intake should be adequate to maintain levels at least greater than 20 ng/mL [2]. Repletion of vitamin D deficiency in PHPT has been shown to lower bone turnover [3]. Therapy with oral bisphosphonates (alendronate and risedronate), estrogen, or raloxifene has been shown to have beneficial

effects on bone density and bone turnover in PHPT [2]. No long-term trials have been performed with fracture outcomes. In one study, surgery was more beneficial to bone density than risedronate [4]. No consistent effects have been seen on serum calcium with use of oral bisphosphonates or raloxifene in PHPT. Therefore, it seems reasonable to use bisphosphonates, especially alendronate which is the best studied in PHPT, to attenuate the effects of PHPT on bone density in patients with osteoporosis or high fracture risk. The duration of bisphosphonate therapy use in PHPT has not been studied and may be determined by periodic assessment of fracture risk and bone density. A drug holiday may be appropriate as in general postmenopausal osteoporosis.

Cinacalcet is a calcimimetic drug that increases the sensitivity of the calcium-sensing receptor on the parathyroid glands, thereby reducing PTH secretion and serum calcium. In a recent short-term double-blind randomized placebo-controlled trial, cinacalcet normalized calcium in 76 % of PHPT subjects and PTH was reduced [5]. A pooled analysis similarly demonstrated that cinacalcet was effective in lowering calcium across a spectrum of PHPT including failed parathyroidectomy [6]. However, cinacalcet did not have demonstrable benefits on bone density. A small prospective study suggests that cinacalcet with appropriate diet may lower the rate of formation of kidney stones in PHPT [7]. Symptom improvement in PHPT treated with cinacalcet has not been extensively studied but a small study of 17 patients reported improvement in Medical Outcomes Study (MOS) Short Form 36 (SF-36) scores with cinacalcet treatment [8]. As with bisphosphonate use in PHPT, the potential long duration of use of cinacalcet in this setting is unstudied. The high incidence of side effects including nausea, vomiting, and diarrhea may limit use. Hypocalcemia may develop; however, dose titration starting with 30 mg twice daily and increasing every 3 weeks did not result in hypocalcemia in a recent trial in PHPT [5]. It is also important to remember that drug interactions

may occur related to strong inhibition of CYP2D6 and as a substrate of CYP3A4. The relatively high cost of cinacalcet may be an additional barrier for some patients.

Combination therapy with bisphosphonate and cinacalcet is an attractive option in PHPT as it would provide bone density improvement and calcium lowering. Neither agent alone can achieve this. Retrospective studies report benefits to both calcium and bone density with the combination but prospective trials or controlled trials are lacking [2].

## Management

The lack of localization on imaging precluded considering an additional operation. This may be due to parathyromatosis which is often difficult to visualize (see Chap. 11). Her degree of hypercalcemia and symptoms were considered as reasons to initiate medical therapy, with a goal of normalizing her calcium and determining if that improved symptoms. She was advised about calcium and vitamin D intake and prescribed cinacalcet 30 mg once daily. This was titrated up to 30 mg twice daily and calcium levels normalized, and she reported improvement in her fatigue. Bisphosphonates were not initiated due to her near normal bone density.

## Outcome

Two years later, she continues on cinacalcet and calcium remains normal although PTH is persistently mildly elevated. Bone density is unchanged. It is not clear how often to monitor bone density on cinacalcet therapy. She is at risk of bone loss as she enters the menopausal transition.

**Clinical Pearls/Pitfalls**

- Surgery remains the treatment of choice for PHPT patients needing treatment.
- Bisphosphonates, particularly alendronate, have been shown to improve bone density in PHPT, but may not be superior to surgery in improving bone density.
- Cinacalcet can lower or normalize serum calcium in PHPT but does not improve bone density.
- Combination therapy with both alendronate and cinacalcet may be attractive for patients with osteoporosis or high fracture risk and significant hypercalcemia.

**Conflict of Interest** All authors state that they have no conflicts of interest.

## References

1. Richards ML, Thompson GB, Farley DR, Grant CS. Reoperative parathyroidectomy in 228 patients during the era of minimal-access surgery and intraoperative parathyroid hormone monitoring. Am J Surg [Comp Stud]. 2008;196(6):937–42. discussion 42-3.
2. Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. J Clin Endocrinol Metab [Consens Dev Conf]. 2014;99(10):3607–18.
3. Grey A, Lucas J, Horne A, Gamble G, Davidson JS, Reid IR. Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. J Clin Endocrinol Metab [Res Support, Non-US Gov't]. 2005;90(4):2122–6.
4. Tournis S, Fakidari E, Dontas I, Liakou C, Antoniou J, Galanos A, et al. Effect of parathyroidectomy versus risedronate on volumetric bone mineral density and bone geometry at the tibia in

postmenopausal women with primary hyperparathyroidism. J Bone Miner Metab [Comp Stud Res Support, Non-US Gov't]. 2014;32(2):151–8.
5. Khan A, Bilezikian J, Bone H, Gurevich A, Lakatos P, Misiorowski W, et al. Cinacalcet normalizes serum calcium in a double-blind randomized, placebo-controlled study in patients with primary hyperparathyroidism with contraindications to surgery. Eur J Endocrinol [Multicenter Stud Randomized Control Trial Res Support, Non-US Gov't]. 2015;172(5):527–35.
6. Peacock M, Bilezikian JP, Bolognese MA, Borofsky M, Scumpia S, Sterling LR, et al. Cinacalcet HCl reduces hypercalcemia in primary hyperparathyroidism across a wide spectrum of disease severity. J Clin Endocrinol Metab [Clin Trial Multicenter Stud Randomized Control Trial Res Support, Non-US Gov't. 2011; 96(1):E9–18.
7. Brardi S, Cevenini G, Verdacchi T, Romano G, Ponchietti R. Use of cinacalcet in nephrolithiasis associated with normocalcemic or hypercalcemic primary hyperparathyroidism: results of a prospective randomized pilot study. Arch Ital Urol Androl [Randomized Control Trial]. 2015;87(1):66–71.
8. Marcocci C, Chanson P, Shoback D, Bilezikian J, Fernandez-Cruz L, Orgiazzi J, et al. Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab [Res Support, Non-US Gov't]. 2009;94(8):2766–72.