

# Primary Hyperparathyroidism: A Case Series

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## ABSTRACT

**Introduction:** Primary hyperparathyroidism (PHPT) is an uncommon endocrine disorder characterized by overproduction of parathyroid hormone. It is diagnosed either due to symptoms or by noting an elevated calcium level on laboratory tests drawn for other reasons. There is a suggestion that PHPT may be related to other autoimmune disorders.

**Case Presentation:** We present four cases of PHPT with different symptomatic presentations. Three of the patients had other autoimmune disorders. Three were treated surgically and one elected watchful waiting. We also looked at the incidence rates across 20 family medicine clinics in Wisconsin to determine whether PHPT has increased in frequency.

**Discussion:** All four of our cases presented differently, and 3 had other autoimmune disorders. The incidence in our clinics did not change over the last 5 years.

**Conclusion:** PHPT is an uncommon disorder, but one that primary care clinicians will see in the office. These cases illustrate the variety of presentations of PHPT.

## INTRODUCTION

Primary hyperparathyroidism (PHPT) is an uncommon endocrine disorder characterized by overproduction of parathyroid hormone (PTH) by a parathyroid gland that has lost its normal negative feedback, thus causing hypercalcemia.<sup>1</sup> Here we report 4 cases of PHPT from primary care clinics and review the epidemiology, diagnosis, and treatment of PHPT, as well as discuss a potential association between PHPT and autoimmune disease. After institutional review board (IRB) approval and patient consent was obtained, a chart review on each of the 4 patients was performed. A search of the electronic health record was performed to find the annual incidence rate of PHPT in 20 academic family medicine clinics in Wisconsin.

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## CASE PRESENTATIONS

### Case 1

A 65-year-old white woman presented to her primary care clinician with progressing hand pain. She was referred to the rheumatology clinic where she was diagnosed with osteoarthritis. During that consult, a hand x-ray was taken and chondrocalcinosis was seen in the cartilage in her hand. During a subsequent workup that included laboratory studies, her serum calcium was 10.4 mg/dL (reference range 8.5-10.2 mg/dL) and serum PTH level was 72 pg/mL (reference range 14-72 pg/mL). Subsequent 24-hour urine calcium was 185.4 mg (reference range 100-250 mg). Her medications at that time included fluoxetine,

trazodone, and valcyclovir. She had normal renal function. Her primary care clinician ordered a bone density scan that showed osteopenia. After being diagnosed with PHPT, she elected to pursue watchful waiting with regular lab studies to monitor her calcium and a repeat bone density scan to monitor decreases in her bone density.

### Case 2

A 34-year-old white woman with a history of juvenile rheumatoid arthritis and Crohn's disease that was discovered subsequent to her being diagnosed with PHPT presented with calcaneal and metatarsal stress fractures. Her initial evaluation included a normal serum calcium of 8.6 mg/dL, but PTH elevated at 96.3 pg/mL. Subsequent 24-hour urine calcium was normal. She had normal renal function. She elected to undergo parathyroidectomy. Her recovery was complicated by symptomatic low calcium levels caused by hungry bone syndrome, a condition where the decrease in PTH leads to reduced bone resorption and increased bone formation that increases the influx of calcium to the bones and a decreases serum calcium. The patient presented with symptoms of hypocalcemia that improved within 6 months of intravenous calcium infusions.

**Table.** Primary Hyperparathyroidism (PHPT) Cases in 20 Academic Family Medicine Clinics Around Wisconsin

	2009	2010	2011	2012	2013	2014	Total
Unique patients	110,348	110,421	105,984	107,735	109,576	110,173	654,237
Number of PHPT cases	57	28	34	25	37	44	225
Rate per 100,000 patients	51.655	25.357	32.080	23.205	33.767	39.937	34.391

**Case 3**

A 38-year-old white woman with a history of Graves' disease that was treated with a total thyroidectomy presented with repeated episodes of kidney stones with normal urinary calcium measurements and renal function. Medication at this time included levothyroxine. During an endocrine workup for her kidney stones, her serum PTH was 173.7 pg/mL, while her serum calcium was 9.4 mg/dL. She underwent parathyroidectomy. Her recovery was uncomplicated and her PTH is now in the normal range.

**Case 4**

A 56-year-old white woman with a history of Sjögren's syndrome presented with hypercalcemia that was discovered during the workup of vague abdominal symptoms including abdominal pain and constipation. Her PTH level was subsequently measured at 94.4 pg/mL and her serum calcium was 10.4 mg/dL. She had normal renal function as well. She was referred to an endocrine surgeon and elected to have a parathyroidectomy. Surgery was performed, and after an uncomplicated recovery, PTH and serum calcium were in the normal range. However, her abdominal symptoms improved only marginally.

**DISCUSSION****Epidemiology**

The incidence of PHPT has varied significantly over the past 50 years. Historically, this disease has been rare. The incidence spiked in the 1970s with the introduction of automated lab assays that included serum calcium levels on common panels. After decreasing in the 1980s, the incidence again spiked in the late 1990s with the advent of bone density screenings for osteoporosis.<sup>2</sup>

Current estimates of prevalence of PHPT range from 182 to 672 per 100,000 people.<sup>3-7</sup> The yearly incidence rates vary by sex and race, with women being affected 2 to 3 times more often than men (85.3/100,000 person-years vs 29.6/100,000 person-years)<sup>2</sup> and black patients affected at higher rates than other races.<sup>8</sup>

We looked at the PHPT cases at 20 academic family medicine clinics in Wisconsin. Data was retrieved from the electronic medical record using the ICD-9 code 252.01 for PHPT in the problem list or from billing data. Dividing the number of cases by the total unique patients seen at the clinics, we found an average yearly incidence rate of 34.4 PHPT cases/100,000 patients. There was no clear trend seen in the number of cases over the 5-year period (Table).

**Clinical Presentation**

Hypercalcemia is often the first laboratory abnormality detected in the majority of patients with PHPT.<sup>9,10</sup> If the hypercalcemia caused by PHPT is not corrected, the disease can progress to include the classic symptomatic presentation of PHPT, which is summarized in the phrase "bones, stones, abdominal moans, psychic groans." "Bones" refers to a decrease in bone density caused by PTH activating osteoclasts that can lead to pathological fractures. "Stones" refers to kidney stones caused by increased calcium excreted in the urine. "Abdominal moans" refers to indistinct abdominal symptoms such as constipation, abdominal pain, nausea, and loss of appetite. "Psychic groans" includes neuropsychiatric symptoms such as cognitive dysfunction, depression, and lethargy.<sup>11</sup> While PHPT is detected while asymptomatic in many patients, some patients still present for the first time with symptomatic disease. Three of our cases presented with classic symptoms of PHPT. Case 2 presented with "bones" (stress fractures), Case 3 with stones, and Case 4 with abdominal moans.

**Diagnosis**

Elevated serum calcium is usually the first sign of PHPT detected. The calcium measurement should be repeated and albumin should be measured and used to calculate the corrected calcium. A history and physical exam should be done to look for the signs and symptoms of hypercalcemia. Once hypercalcemia is confirmed, intact PTH levels should be checked. If PTH is low, consider other causes of hypercalcemia, such as malignancy. If PTH is in the normal range or elevated, family history and 24-hour urine calcium concentration with creatinine clearance should be done to rule out familial hypocalciuric hypercalcemia (FHH). If the calcium/creatinine ratio is below 0.01, FHH should be considered; if not, PHPT is more likely. The primary care clinician can refer directly to an endocrine surgeon, or to an endocrinologist if the diagnosis of PHPT is in question.<sup>12,13</sup>

**Treatment**

Medical management of PHPT can be used to prevent some of the effects of the disease. Cinacalcet is a drug that acts allosterically to increase the sensitivity of the calcium-sensing receptor in parathyroid tissue and can be used to reduce serum calcium, but has no effect on bone mineral density.<sup>14</sup> It can be used to reduce calcium levels in people who are not surgical candidates. Bisphosphonates have been shown to improve bone mineral

density and can be used in combination with cinacalcet.<sup>15</sup> The only curative treatment for PHPT is surgery. The most recent expert consensus statement includes the following as indications for surgery: (1) if a patient is symptomatic or has significant signs of disease such as decreased bone mineral density or nephrolithiasis; (2) patient age under 50; (3) serum calcium levels more than 1 mg/dl above the upper limit of normal; (4) patient is unable or unwilling to undergo medical management or surveillance.<sup>16,17</sup> Medical surveillance is appropriate in patients who are asymptomatic and usually involves monitoring bone mineral density and serum calcium and PTH levels at regular intervals.

### Possible Autoimmune Relationship

Three of the 4 patient cases that were reviewed also had 1 or more autoimmune diagnoses. Case 2 had a long history of juvenile rheumatoid arthritis and was diagnosed with Crohn's disease after undergoing parathyroid surgery. Case 3 has a personal and family history of Graves' disease, and Case 4 has Sjögren's syndrome.

A literature search of PubMed was performed using the MeSH headings for PHPT and autoimmune disease. The prevalence of PHPT was found to be about 4 times higher in a cohort of patients with chronic atrophic autoimmune gastritis (CAAG) than in the general population, while the prevalence of CAAG in a cohort of PHPT patients was found to be 3 times higher than the general population.<sup>18</sup> Another study found, in a cohort of 2267 patients with Hashimoto's thyroiditis, a PHPT prevalence of 1.89% compared to 0.182% to 0.6.72% in the general population.<sup>19</sup> Finally, some patients with PHPT have been shown to have anticalcium sensing receptor auto-antibodies.<sup>20</sup> Future research should further evaluate any relationship between PHPT and autoimmune disease.

### CONCLUSION

Here we report 4 cases of PHPT that presented to their primary care clinician. While we did not see a temporal trend in our incidence data, the incidence reported by others continues to change. The manner in which PHPT presents is also changing, from a disease that presents with the classic syndrome of "bones, stones, moans, and groans" to an asymptomatic disease presenting with hypercalcemia without other symptoms. When PHPT is diagnosed, medical treatments can limit the symptoms and effects of the disease, but parathyroidectomy is the only curative treatment. Three out of the 4 cases above had autoimmune diseases comorbid with PHPT (juvenile rheumatoid arthritis, Crohn's disease, Graves' disease, and Sjogren's syndrome). Increased coincidence for PHPT and other autoimmune diseases has been reported. More research is needed to determine if there is a link between autoimmune pathology and PHPT.

**Funding/Support:** None declared.

**Financial Disclosures:** None declared.

**Disclaimer:** Dr Schragar, associate editor of the *WMJ*, was not involved in the editorial review of or decision to publish this article.

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*WMJ* (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

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