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Primary Hyperparathyroidism

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Primary Hyperparathyroidism

- In primary hyperparathyroidism (PHPT), an enlargement of one or more of the parathyroid glands causes overproduction of the parathyroid hormone. This hormone regulates the level of calcium in the body, including the release of calcium from bones and the excretion of calcium in the urine. It also increases calcium absorption in the duodenum by changing 25(OH)D to the active form of vitamin D: 1,25(OH)₂D. Abnormally high parathyroid hormone levels typically result in hypercalcemia.
- The most common cause of PHPT is parathyroid adenoma, found in 80% of patients. Hyperplasia is involved in most other cases, and carcinoma is a rare cause.

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National Institute of Diabetes and Digestive and Kidney Diseases. Primary Hyperparathyroidism. Available at

<https://www.niddk.nih.gov/health-information/endocrine-diseases/primary-hyperparathyroidism>. Accessed August 28, 2018.

Mayo Clinic. Hyperparathyroidism. Available at <https://www.mayoclinic.org/diseases-conditions/hyperparathyroidism/symptoms-causes/syc-20356194>. Accessed August 28, 2018.

Velez RP et al. Simplifying the Complexity of Primary Hyperparathyroidism. *The Journal for Nurse Practitioners* 2016; 12(5): 346–352.

Epidemiology of PHPT

- In the United States, primary hyperparathyroidism is the most common cause of hypercalcemia encountered in ambulatory care. About 100,000 people develop PHPT each year. It is diagnosed most often in people between age 50 and 60, and women are affected two to three times more often than men. Postmenopausal women have the highest incidence.

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Clinical Presentation

- One of the most common manifestations of PHPT is nephrolithiasis. In the United States, 15% to 20% of patients with PHPT present with kidney stones, due to high calcium levels in the glomerular filtrate.
- However, in addition to maintaining bone health, calcium plays a role in metabolic processes, nerve impulse conduction, muscle contraction, and the clotting cascade. Abnormally elevated calcium can affect the nervous, renal, cardiac, and gastrointestinal systems.

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Clinical Presentation, Continued

- Patients may therefore present with other renal, musculoskeletal, gastrointestinal, and psychiatric symptoms. (“Stones, bones, abdominal groans, psychiatric moans.”) These include:
 - Anorexia
 - Nausea/vomiting
 - Constipation
 - Insomnia
 - Depression
 - Fatigue/muscle weakness
 - Arthritis
 - Bone and/or joint pain
 - Bone demineralization/ fractures
 - Polydipsia and polyuria

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Clinical Presentation, Continued

- Such symptoms are typically seen in patients whose calcium levels rise rapidly. If calcium levels increase slowly, patients may adapt to the change and have no symptoms. In resource rich countries, as many as 85% of patients with PHPT may be asymptomatic.
- In addition, some patients with mild PHPT may have high levels of parathyroid hormone but normal levels of calcium (normocalcemic hyperparathyroidism).

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Diagnosing PHPT

- Hypercalcemia in conjunction with abnormally elevated or inappropriately normal parathyroid hormone levels makes PHPT the most likely diagnosis. Calcium and parathyroid hormone levels should be tested at the same time because individual levels fluctuate quickly. Hypercalcemic patients may occasionally have normal calcium levels, so repeated calcium measurements may be required.
- Measurement of serum calcium should be adjusted for albumin, as 40% of calcium is bound to serum proteins, predominantly albumin. If the adjusted serum calcium is normal but parathyroid hormone is elevated, serum ionized calcium should be measured. PHPT can present with an elevated ionized calcium despite a normal albumin-adjusted serum calcium.

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Diagnosing Normocalcemic PHPT

- Patients with normocalcemic PHPT will have elevated parathyroid hormone but normal levels of serum and ionized calcium. To establish a diagnosis of normocalcemic PHPT, secondary causes of elevated parathyroid hormone should be excluded, such as primary hypercalciuria, malabsorption syndromes, use of loop diuretics, bisphosphonates, or denosumab therapy.
- In addition, renal function and vitamin D status should be assessed with measurements of creatinine and 25-hydroxyvitamin D. Elevated serum parathyroid hormone with consistently normal albumin-adjusted calcium and ionized calcium, normal serum 25-hydroxyvitamin D, and well-maintained renal function (eGFR >60 mL/min/1.73 m²) supports the diagnosis of normocalcemic PHPT.
- Normocalcemic PHPT may progress to classic PHPT over time.

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Ruling Out Familial Hypocalciuric Hypercalcemia

- Familial hypocalciuric hypercalcemia (FHH), an autosomal dominant disorder of the renal calcium-sensing receptor, can mimic PHPT. A 24-hour urinary calcium level is important to distinguish PHPT from FHH. A diagnosis of FHH should be considered in patients with long-standing hypercalcemia, urinary calcium levels less than 100mg/24 hours, and a calcium-to-creatinine clearance ratio less than 0.01.

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Additional Tests

- PHPT reduces bone mineral density and may increase the risk for fragility fractures. Dual-energy x-ray absorptiometry assessment is appropriate for all patients with PHPT and should be performed to screen for weakened bones and skeletal problems. Bone mineral density should be measured at the lumbar spine, hip, and distal radius. The 24-hour urine calcium test is also recommended.
- In patients with asymptomatic PHPT, abdominal imaging may be useful for detecting nephrocalcinosis or nephrolithiasis.

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Treatment: Surgery

- Surgery to remove abnormal parathyroid tissue is the only known cure for PHPT. Symptomatic patients with PHPT should be advised to undergo surgery. Surgery is also recommended for asymptomatic patients with the following indications:
 - Age < 50 years
 - Serum calcium > 1 mg/dL (> 0.25 mmol/L) above upper limit of normal
 - Bone mineral density T-score of ≤ 2.5 (osteoporosis) or a low-energy fracture on imaging study
 - Creatinine clearance reduced to < 60 mL/min, or 24-hour urine for calcium > 400 mg/day and increased stone risk by biochemical stone risk analysis, or nephrolithiasis or nephrocalcinosis on imaging study
- Even when there is no specific indication for surgery, it is an established and appropriate treatment because it is the only known cure.

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Treatment: Surgery

- Minimally invasive parathyroid (MIP) surgery to remove abnormal glands has become the standard of care. With an experienced surgeon, cure rates with minimally invasive procedures exceed 95%, and the complication rate is low (1% to 3%). A general or local anesthesia is used, and patients can usually be discharged home 2 hours after surgery. Patients who require extensive neck exploration or excision of all four glands may require open surgery.
- Parathyroid hormone (PTH) monitoring during surgery can confirm the removal of all hyperfunctioning parathyroid glands, as the half-life of the hormone is 3-5 minutes. If the PTH level decreases by at least 50 % and falls into the normal range following resection, this confirms that adequate tissue has been resected and that no further exploration is necessary. When an image-guided focused parathyroidectomy is planned, intraoperative PTH monitoring is recommended to avoid missing multi-gland disease.
- Surgery has been shown to normalize calcium and parathyroid hormone levels, reduce the risk of kidney stones, and improve bone remodeling and skeletal health. It may also have other cardiovascular, renal, neurological, and gastrointestinal benefits.

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Treatment: Repeat Surgery

- Repeat surgery may be necessary in up to 5% of patients who develop persistent PHPT due to incomplete resection of abnormal parathyroid tissue.
- In addition, up to 8% of patients will develop recurrent disease within 3 to 11 years and require repeat surgery.
- In patients with persistent PHPT, a diagnosis of familial hypocalciuric hypercalcemia (FHH) should be considered and ruled out before repeat surgery.

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When Surgery Is Not an Option

- Surgery is not recommended in patients for whom the risks outweigh the benefits, such as those with severe or overriding medical illnesses. In addition, some patients will refuse surgery.
- Other situations that may prompt nonsurgical management include:
 - First trimester pregnancy
 - Severely limited cervical access
 - Prior vocal cord paralysis
 - Short expected lifespan

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Monitoring Non-Surgical Patients

- For patients who refuse surgery or in whom it is contraindicated, monitoring can be a safe option for up to 8-10 years. Bone mineral density tests should be performed ever 1-2 years in these patients. Biochemical profiles should be assessed yearly.
- In addition, calcium intake should be recommended without restrictions according to the Institute of Medicine Guidelines, and vitamin D levels should be sufficient.
- Finally, although medical management cannot cure PHPT, it can be an option for non-surgical patients.

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Medical Management

- Currently, the only medication shown to lower serum calcium in patients with PHPT is the calcimimetic agent cinacalcet. Cinacalcet normalizes serum calcium in 70% to 80% of patients with PHPT. However, it has not been shown to impact bone mineral density, hypercalcemic symptoms, kidney stones, or quality of life.
- Close monitoring of serum calcium levels is necessary in patients on cinacalcet because of its adverse effects on QT prolongation, arrhythmias, heart failure, and hypotension.

Marcocci C et al. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab* 2014; 99(10): 3607-18.

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Medical Management

- Bisphosphonates may be used in combination with cinacalcet in patients with T-scores ≤ 2.5 at the lumbar spine, hip, or one-third radius, or who have fragility fractures. These agents have been shown to be effective in preventing decreases in bone mineral density and lowering bone remodeling.
- Many patients with PHPT will have vitamin D deficiency or insufficiency. Normalizing vitamin D is recommended. It has been shown to reduce serum parathyroid hormone levels without increasing serum calcium.

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