Hyperparathyroidism

Through their secretion of parathyroid hormone (PTH), the parathyroid glands are primarily responsible for maintaining extracellular calcium concentrations. Hyperparathyroidism is a disease characterized by excessive secretion of PTH, an 84–amino acid polypeptide hormone. The secretion of PTH is regulated directly by the plasma concentration of ionized calcium. The main effects of PTH are to increase the concentration of plasma calcium by increasing the release of calcium and phosphate from bone matrix, increasing calcium reabsorption by the kidney, and increasing renal production of 1,25-dihydroxyvitamin D-3 (calcitriol), which increases intestinal absorption of calcium. Thus, overproduction of PTH results in elevated levels of plasma calcium. PTH also causes phosphaturia, thereby decreasing serum phosphate levels. Hyperparathyroidism is usually subdivided into primary, secondary, and tertiary hyperparathyroidism.

Usually, 4 parathyroid glands are situated posterior to the thyroid gland. A small number of patients have 3, 5, or occasionally, more glands. The glands are identified based on their location as right or left and superior or inferior.

The inferior glands are derived from the third pharyngeal pouch. This structure is also the embryologic origin of the thymus. Therefore, the inferior glands originate more cephalad than the superior glands, but they migrate along with the thymus to finally become situated more inferiorly than the superior glands. Because of their embryologic association with the thymus, the inferior glands are often found adjacent to or within the thymus. They are usually located near the inferior pole of the thyroid.

The superior glands are more consistent in location, usually found just superior to the intersection of the inferior thyroid artery and the recurrent laryngeal nerve. The superior glands are derived embryologically from the fourth pharyngeal pouch. This structure also gives rise to the C cells of the thyroid gland. Because of their embryologic origin, the superior glands are occasionally found within the substance of the thyroid gland. Ectopic locations of parathyroid glands are discussed in more detail in "Primary Hyperparathyroidism," under surgical care.

Definition of the problem

Primary hyperparathyroidism is the unregulated overproduction of PTH resulting in abnormal calcium homeostasis.

Frequency

The prevalence of primary hyperparathyroidism is slowly decreasing. Most recently, the prevalence is reported to be approximately 4 cases in 100,000 persons. Primary hyperparathyroidism affects women approximately twice as frequently as men. Prevalence increases with age, but hyperparathyroidism can affect persons of all ages, including children.

Etiology

In approximately 85% of cases, primary hyperparathyroidism is caused by a single adenoma. In 15% of cases, multiple glands are involved (ie, either multiple adenomas or hyperplasia). Rarely, primary hyperparathyroidism is caused by parathyroid carcinoma. The etiology of adenomas or hyperplasia remains unknown in most cases. Familial cases can occur either as part of the multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a), hyperparathyroid-jaw tumor (HPT-JT) syndrome, or familial isolated hyperparathyroidism (FIHPT). Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism also belong to this category. The molecular genetic basis of MEN 1 is an inactivating mutation of the *MEN1* gene, located on chromosome band 11q13. MEN 2a is caused by a germline mutation of the *Ret* proto-oncogene on chromosome 10. Germline mutation of *HRPT2* localized on chromosome arm 1q is responsible for HPT-JT, while FIHPT is genetically heterogeneous.

Pathophysiology

In primary hyperparathyroidism due to adenomas, the normal feedback on PTH production by extracellular calcium seems to be lost, resulting in a change in the set point. However, this is not the case in primary hyperparathyroidism from parathyroid hyperplasia. An increase in the cell numbers is probably the cause.

The chronic excessive resorption of calcium from bone caused by excessive PTH can result in osteopenia. In severe cases, this may result in osteitis fibrosa cystica, which is characterized by subperiosteal resorption of the distal phalanges, tapering of the distal clavicles, salt-and-pepper appearance of the skull, and brown tumors of the long bones. This is not commonly seen now. In addition, the chronically increased excretion of calcium in the urine can predispose to the formation of renal stones.

The other symptoms of hyperparathyroidism are due to the hypercalcemia itself and are not specific to hyperparathyroidism. These can include muscle weakness, fatigue, volume depletion, nausea and vomiting, and in severe cases, coma and death. Neuropsychiatric manifestations are particularly common and may include depression, confusion, or subtle deficits that are often characterized poorly and may not be noted by the patient. Increased calcium can increase gastric acid secretion, and persons with hyperparathyroidism may have a higher prevalence of peptic ulcer disease. Rare cases of pancreatitis have also been attributed to hypercalcemia.

Clinical presentation

History

Symptoms related to hyperparathyroidism may include bone pain, pathologic fractures, and nephrolithiasis.

Symptoms related to hypercalcemia may include muscle weakness, volume depletion, polyuria and polydipsia, neuropsychiatric symptoms, peptic ulcer disease, and pancreatitis.

Physical Examination

Physical examination findings are usually noncontributory. Examination may reveal muscle weakness and depression. A palpable neck mass is not usually expected with hyperparathyroidism, although in rare cases, it may indicate parathyroid cancer.

Differential diagnosis

The causes of hypercalcemia that result in a concomitantly elevated PTH level are few. These include familial benign (hypocalciuric) hypercalcemia (FHH) lithium-induced hypercalcemia, and tertiary hyperparathyroidism. A cautionary note is that a minority of patients (i.e., 10-15%) with hyperparathyroidism have PTH levels at the high end of the reference range, which is inappropriately high in the presence of elevated calcium. A subset of patients has calcium levels within the reference range with elevated PTH, which is called normocalcemic hyperparathyroidism. However, for considering this diagnosis, all potential causes of secondary hyperparathyroidism (eg, low calcium intake, GI disorders, renal insufficiency, vitamin D deficiency, hypercalciuria of renal origin) should be excluded.

Secondary and tertiary hyperparathyroidism are typically diagnosed on the basis of their clinical context. Cancer-induced hypercalcemia is usually associated with a low PTH level but possibly a high PTH-related peptide level.

Laboratory studies

Total serum calcium and albumin levels or ionized calcium levels should be measured. Hypercalcemia should be documented on more than one occasion before a diagnostic workup is undertaken.

Testing of the intact PTH level is the core of the diagnosis. An elevated intact PTH level with an elevated ionized serum calcium level is diagnostic of primary hyperparathyroidism. Older assays measured portions of the PTH molecule, such as the C-terminal or N-terminal. These older assays should no longer be used in routine clinical practice. The current assay uses 2 different antibodies to 2 different epitopes; therefore, only the intact molecules are detected. A second-generation assay that measures the full-length molecule

should be used. This is important in detecting only active PTH, particularly when PTH levels are low.

A 24-hour urine calcium measurement is necessary to rule out FHH. A markedly elevated level is an indication for surgery.

Imaging studies

Imaging studies are not used to make the diagnosis of primary hyperparathyroidism (which is based on laboratory data) or to decide on surgical therapy (which is based on clinical criteria). Imaging studies are used to guide the surgeon once surgical therapy has been decided. If a limited parathyroid exploration is to be attempted, a localizing study is necessary. Other uses of imaging studies in the initial evaluation of a patient with primary hyperparathyroidism are controversial.

For many patients, the recommendation remains for complete parathyroid exploration with resection of all involved glands. Many surgeons agree that imaging studies are not required when this surgical treatment is chosen. However, in patients who have recurrent or persistent hyperparathyroidism after a previous surgical exploration, an imaging test to localize involved glands is definitely indicated. As more experience is gained with technetium Tc 99 sestamibi scanning, use of this modality to guide surgical therapy and even to confirm the diagnosis itself is becoming routine.

The best initial test is sestamibi nuclear medicine scanning. This radionuclide is concentrated in parathyroid tissue. The scan is highly specific for abnormal parathyroid tissue. It also has a sensitivity of greater than 90% in the case of solitary adenomas. The main weakness of this test is in diagnosing multiglandular disease. In this case, sensitivity drops to approximately 55%. When combined with single-photon emission computed tomography scanning, it can be used effectively to localize ectopic and usual parathyroid adenomas and, therefore, is the imaging study of choice.

Ultrasonography of the neck may be equivalent or superior to sestamibi scanning. However, it is operator-dependent and has been reported to have widely varying degrees of accuracy. One advantage of neck ultrasonography is that it can be performed rapidly by the clinician at the time of the initial evaluation.

CT scanning and MRI have also been used, although they have now largely been replaced by sestamibi scanning. CT scanning has inadequate sensitivity. MRI can be useful, particularly in the case of recurrent or persistent disease and in ectopic locations such as the mediastinum.

A bone mineral density test is a useful tool to document osteopenia. Note that hyperparathyroidism preferentially affects the cortical bone at the radius (distal third).

Procedures

Bilateral internal jugular vein sampling is used to help localize ectopic parathyroid adenomas; however, this technique should generally be reserved for centers with specialists and for selected patients.

Treatment

Medical care

The diet of individuals with primary hyperparathyroidism should include around 1200-1500 mg of calcium per day. Also, 400 IU of vitamin D per day is reasonable. Estrogen therapy in postmenopausal women has been shown to cause a small reduction in serum calcium and increases in BMD, with stable PTH. However, risks are associated with estrogen replacement. Raloxifene may be an alternative. Alendronate has also been shown to increase the spine BMD in patients with primary hyperparathyroidism. Calcimimetic drugs may be an alternative in the future.

Other medical therapy is limited to the treatment of hypercalcemia itself. In the acute setting, this can be accomplished by the use of intravascular volume expansion with sodium chloride and loop diuretics such as furosemide once the intravascular volume is restored. In rare cases, hypercalcemia has been treated with bisphosphonate therapy as a temporary measure prior to surgical treatment.

Surgical care

- Indications for surgery

    o Symptomatic hyperparathyroidism should be treated by surgical excision of the abnormal glands.

    o Some clinicians advocate surgical therapy in all patients with primary hyperparathyroidism, modified only for those patients who are not able to tolerate surgery. They argue that the operation is generally well tolerated and such treatment prevents complications (eg, osteoporosis) and may reverse symptoms that patients often do not realize they have (eg, fatigue, depression). Others advocate a nonsurgical approach whenever possible, such as in patients with a calcium level less than 11.5 mg/dL, patients with no apparent symptoms, and patients who have normal 24-hour urine calcium excretion and no osteoporosis.

    o A National Institutes of Health (NIH) Workshop on Asymptomatic Primary Hyperparathyroidism in 2002 revisited the key management issues addressed at the 1990 NIH Consensus Development Conference. They recommended new guidelines for surgery and the conservative approach of monitoring patients

who do not meet the criteria for surgery. The indications for surgery as per the 2002 guidelines are as follows:

- 1.0 mg/dL above the upper limit of the reference range for serum calcium

- 24-hour urinary calcium excretion greater than 400 mg

- A 30% reduction in creatinine clearance

- Bone mineral density T-score below -2.5 at any site

- Age less than 50 years

o For monitoring of patients with asymptomatic hyperparathyroidism who do not undergo surgery, the following are recommended: serum calcium and creatinine levels every 6 months and annual bone mineral density (all 3 sites).

- Choice of surgical treatment

o The standard operative approach is complete neck exploration with identification of all parathyroid glands and removal of all abnormal glands. In the case of 4-gland hyperplasia, a 3.5-gland (subtotal) parathyroidectomy is performed. Approximately 50-70 mg of the most normal-appearing tissue is left behind. A nonabsorbable suture is left as a tag to identify the gland should reoperation be necessary.

o Approximately 85% of cases of primary hyperparathyroidism are caused by a single adenoma. Therefore, most patients who undergo full neck exploration to evaluate all parathyroids endure some unnecessary dissection. Rather than explore all parathyroid glands, a newer technique, directed parathyroidectomy, has evolved. This technique relies on preoperative imaging studies to localize the abnormal gland. The surgeon then removes only that gland, without visualizing the other glands.

o With either sestamibi scanning or ultrasonography, an abnormal parathyroid may be detected preoperatively in 70-80% of cases. However, neither technique is reliable for detecting multiple abnormal glands. Therefore, an additional method is required to confirm that no other abnormal glands are present after excision of the imaged lesion.

o For this purpose, many centers have begun to use the intraoperative PTH assay. Because the plasma half-life of PTH is only approximately 4 minutes, the level falls quickly after resection of the source. If the level fails to fall after resection of the identified abnormal gland, the procedure is extended to allow for further exploration. However, the intraoperative PTH

assay is expensive and is usually available only in centers that perform a high volume of parathyroidectomies.

- o A few authors have advocated radio-guided parathyroidectomy, detecting the labeled sestamibi in the abnormal gland using a handheld probe. The excised radioactivity in the abnormal parathyroid is then compared with the remaining background to confirm excision of all affected glands. However, most centers have abandoned this technique because (1) if the gland labels well with sestamibi, use of the handheld probe intraoperatively is unnecessary in most cases and (2) the use of background counts to confirm complete excision of all abnormal tissue has not been well validated.

- o Use of directed parathyroidectomy results in a more limited operation for most patients, resulting in a more rapid recovery. However, it may yield a higher persistence rate than complete neck exploration, and it probably should be performed only in centers with the capability to perform the intraoperative PTH assay.

- o For familial disease, such as MEN 1, total parathyroidectomy is performed with autotransplantation to the forearm and cryopreservation of some parathyroid tissue.

- Preoperative care

  - o Parathyroidectomy is usually well tolerated. The main risks are those associated with anesthesia. Although local anesthesia has been used successfully for this procedure, especially in the directed approaches where a single adenoma is localized preoperatively, general anesthesia is used most commonly.

  - o In patients in whom hypercalcemia (and, therefore, dehydration) has been severe, special attention must be directed to perioperatively restoring the fluid balance.

  - o Neck mobility must be assessed to ensure proper positioning in the operating room.

  - o If the patient's voice is normal, preoperative documentation of vocal cord function is not necessary.

- Intraoperative details

  - o Complete parathyroid exploration

    - ▪ The most critical aspect to ensure success in this operation is identification of all 4 parathyroid glands and removal of all abnormal glands.

- The patient is placed in the lawn-chair position with the neck extended over a transversely placed shoulder roll. This position allows full exposure of anterior neck structures and improves venous drainage.

- A low transverse incision placed within the skin creases provides the best cosmetic result. The length of the incision must be adequate to allow thorough exploration of all potential locations of the parathyroid glands; however, given the elasticity of the neck skin flaps, a 3- to 5-cm incision allows safe identification of important structures.

- After hemostasis of the skin incision is obtained, subplatysmal flaps are developed superiorly to the notch of the thyroid cartilage and inferiorly to the flat portion of the manubrium. The sternohyoid and sternothyroid (strap) muscles are separated in the midline to expose the thyroid gland. If preoperative localization studies suggest a parathyroid adenoma, that side is approached first.

- Frequently, a middle thyroid vein may require ligation to ensure adequate mobilization of the thyroid lobe. The thyroid lobe is elevated off the common carotid artery and retracted medially. The inferior thyroid artery is identified after blunt and sharp dissection of the areolar tissue anteriorly and medially to the common carotid artery and posteromedially to the thyroid lobe. The recurrent laryngeal nerve is identified next, inferior and lateral to the lower lobe of the thyroid gland.

- The intersection of the inferior thyroid artery and the recurrent laryngeal nerve is an important landmark because most parathyroid glands, superior and inferior, are located within 2 cm of this area. The superior parathyroid glands are located dorsal to the upper two thirds of the thyroid lobe and posterior to the recurrent laryngeal nerve. The inferior glands, which are less consistent in location, can usually be found inferior to the inferior thyroid artery and ventral to the recurrent laryngeal nerve. They are usually within 1 cm of the inferior lobe of the thyroid gland.

- Abnormally enlarged glands are excised after confirmation of the normal size of other glands. During excision, avoiding capsular rupture of the abnormal gland is important because this may be associated with implantation of parathyroid cells in the operative site and subsequent parathyromatosis. Parathyroids may be identified by highly experienced surgeons based on appearance and location. In most cases, identification of

the parathyroid glands should be confirmed histologically by frozen section examination. In all cases of subtotal or total parathyroidectomy with autotransplantation, parathyroid tissue must be cryopreserved for future autotransplantation if the initial transplants are not functional.

- o Directed parathyroidectomy

  - In many respects, the operative technique is similar to that described above for a complete parathyroid exploration. Differences are noted below.

  - Adequate imaging of the abnormal gland prior to surgery is essential. In addition, arrangements for intraoperative measurement of PTH should be confirmed. A line for sampling of peripheral venous blood should be established. Often the distal saphenous vein provides the most convenient access.

  - Some surgeons modify the location of the incision based on the preoperative location of the adenoma. This author prefers a small incision (ie, ~2 cm) in the standard location for a collar incision. This incision can be readily extended should a complete exploration prove necessary.

  - A baseline PTH level is drawn immediately prior to skin incision. Following identification and dissection of the adenoma, a preexcision level is drawn. Manipulation of the gland occasionally causes significant increases in the PTH level. Following excision of the gland, PTH levels are drawn at 5 minutes and 10 minutes postexcision. Criteria for adequate excision are either: a 50% drop in PTH from the baseline level to the 10-minute post-excision level or a 50% drop in PTH from the preexcision level at 10 minutes and a postexcision level below the baseline level.

  - The incision may be closed while the last PTH levels are being processed, but the patient should remain under anesthesia and the sterile field maintained until the PTH assay results are known.

- **Ectopic parathyroid glands**

  - o Occasionally, all parathyroid glands cannot be identified. In such instances, the usual locations are reexamined first because most parathyroid glands are located in typical areas. If parathyroid glands are not identified in those locations, then a systematic search is performed, taking into consideration the path of descent of superior and inferior parathyroid glands.

- Inferior glands may be located in the thyrothymic ligament. They may be difficult to identify, especially after division of the inferior thyroid vein, a maneuver that allows the gland to retract into the superior mediastinum. Another location for ectopic inferior parathyroid glands is the thymus. The thymus can be visualized through a transverse cervical incision by retracting the innominate vein dorsally with a sponge-stick while elevating the manubrium anteriorly. Division of the interclavicular ligament improves visualization in the superior mediastinum.

  - Superior parathyroid glands are usually dorsal to the upper two thirds of the thyroid gland. Occasionally, these glands are adjacent to the superior thyroid vessels. Other locations include the carotid sheath or posterior to the esophagus or pharynx (retroesophageal). Finally, both superior and inferior parathyroid glands may be located aberrantly within the capsule of the thyroid gland. Some surgeons perform a thyroid lobectomy on the side harboring the abnormal gland after an exhaustive search is made in the aforementioned locations. Median sternotomy is rarely required during the initial neck exploration for hyperparathyroidism.

- Postoperative care

  - If a directed parathyroidectomy is performed successfully, most of these patients may be safely discharged the day of surgery. Some practitioners routinely supplement with oral calcium postoperatively.

  - For a full parathyroid exploration, calcium levels must be monitored postoperatively every 12 hours until stabilization. The nadir of serum calcium usually occurs 24-72 hours postoperatively. Many patients become hypocalcemic, but few become symptomatic. Reserve treatment for hypocalcemia unless it is severe or the patient becomes symptomatic.

  - Hypocalcemia after parathyroid surgery may be due to hungry bone syndrome where calcium and phosphorus are rapidly deposited in the bone. This is characterized by hypoparathyroidism and transient, but occasionally severe, hypocalcemia until the normal glands regain sensitivity.

  - If hypoparathyroidism persists, oral supplementation with calcium and vitamin D is required. Calcium citrate or calcium carbonate may be started at 2 tablets 4 times per day. Some patients require more or less. Calcitriol is started at 1 mcg/d for 1 day, 0.5 mcg/d for 2 days, and then 0.25 mcg/d thereafter. Patients in whom an autotransplantation is performed require temporary calcium supplementation.

  - If a recurrent nerve injury is suggested because the patient has developed new hoarseness, immediate laryngoscopy is

indicated. If vocal cord paralysis is observed, immediate reoperation may be warranted to repair a transected nerve because a few of these may regain function. Reexploration after 24-48 hours is not generally indicated because the risks of operating in an inflamed field outweigh the relatively low likelihood of a benefit.

- A potential life-threatening emergency in the postoperative period is the development of an expanding hematoma in the pretracheal space. This complication must be recognized and treated immediately by opening the wound and evacuating the hematoma. If untreated, laryngeal edema may progress rapidly, causing airway obstruction.

- Most small hematomas do not require treatment. A subplatysmal fluid collection may occasionally form, and these are usually treated adequately with a single aspiration. In a few cases, aspiration may need to be repeated. Rarely, a drain may need to be placed for recurrent fluid collections.

Follow-up

Patients are seen 1-2 weeks postoperatively, and serum calcium and PTH levels are obtained. PTH levels may be elevated postoperatively in some patients, but if the serum calcium remains within the reference range it does not indicate persistent disease in most patients.

After the immediate postoperative period, follow-up is limited to periodic determinations of serum calcium levels to detect the persistence or recurrence of disease or hypoparathyroidism.

Secondary hyperparathyroidism

Secondary hyperparathyroidism is the overproduction of PTH secondary to a chronic abnormal stimulus for its production. Typically, this is due to chronic renal failure. Another common cause is vitamin D deficiency.

Frequency

Secondary hyperparathyroidism occurs to some degree in virtually all patients with dialysis-dependent chronic renal failure. Vitamin D deficiency is common and is underdiagnosed.

Etiology

In renal failure, the stimuli for overproduction of PTH are multifactorial. Factors include hypocalcemia, impaired 1,25-dihydroxyvitamin D production by the diseased kidneys, and hyperphosphatemia. Hyperphosphatemia appears to be particularly important in the development of parathyroid

hyperplasia. These stimuli cause multigland hyperplasia, resulting in increased PTH production.

Pathophysiology

Chronic overproduction of PTH in patients with renal failure contributes to the spectrum of bone disease observed in patients on dialysis. In most patients on dialysis, the primary bone disease is osteitis fibrosa cystica, a disease of increased bone resorption caused by elevated PTH levels. Skeletal lesions include subperiosteal bone erosions, usually observed best in the distal phalanges. Likewise, the skull has a classic salt-and-pepper or ground-glass appearance.

Other bone diseases are common in patients on dialysis, but these do not appear directly attributable to hyperparathyroidism.

Clinical presentation

Because virtually all patients with renal failure have hyperparathyroidism to some degree, the clinical presentation is often that of renal failure. In patients with secondary hyperparathyroidism due to vitamin D deficiency, the symptoms are mainly due to the vitamin deficiency (e.g., osteomalacia with increased fracture risk, myopathy [rarely]). In advanced cases of secondary hyperparathyroidism, some patients may have bone pain.

Laboratory studies

All patients with renal failure should be monitored regularly with serum calcium, phosphorous, and PTH levels. Patients with secondary hyperparathyroidism usually have a low-normal calcium and elevated PTH. The phosphate level may vary based on the etiology, trending towards high values in renal insufficiency and low values in vitamin D deficiency.

Imaging studies

Radiographic evaluation is limited to assessments of the bone disease. Obtain radiographs of sites of bone pain. Hand radiographs may show characteristic subperiosteal erosions. Imaging of the parathyroid glands is not indicated unless primary hyperparathyroidism is suggested.

Treatment

Medical care

Unlike primary hyperparathyroidism, medical management is the mainstay of treatment for secondary hyperparathyroidism. Treatment with calcitriol and calcium can either prevent or minimize secondary hyperparathyroidism. Control of the serum phosphate levels with a low-phosphate diet and phosphate-binding agents is essential.

Patients with predialysis renal failure, ie, those with early-to-moderate renal failure, usually have a modest elevation of PTH levels. Suppression of PTH secretion with low-dose calcitriol (i.e., 0.125 mcg/d) may prevent subsequent parathyroid gland hyperplasia and secondary hyperparathyroidism; however, calcitriol therapy must be monitored carefully to ensure that hypercalcemia is not induced.

Patients with dialysis-dependent chronic renal failure require calcitriol, oral calcium supplementation, calcium in the dialysate, aluminum-free phosphate binders, and cinacalcet (Sensipar) to maintain levels of serum calcium and phosphate within their reference ranges. Because patients on dialysis are relatively resistant to the actions of PTH, a PTH level within the reference range is not necessarily desirable. A recent survey of patients on dialysis using this therapy found that 50% had PTH levels at least 3 times the reference range.

Surgical care

Indications include bone pain or fracture, pruritus, and calciphylaxis

Failure of medical therapy to control hyperparathyroidism is a soft indication for surgery. Generally, if PTH levels of greater than 400-500 pg/mL persist after correction of serum calcium and phosphorus levels and evidence of progressive bone disease is present, parathyroidectomy may be considered.

- Intraoperative details
    - All 4 glands must be exposed, and biopsies are taken if needed to ensure correct identification. In most cases, diffuse hyperplasia is encountered, although the size of the glands can be significantly heterogeneous.
    - The procedure of choice is either total parathyroidectomy with autotransplantation or 3.5-gland parathyroidectomy. In either case, a thymectomy must be included. A 1991 article by Rothmund et al reported a randomized controlled trial of total versus subtotal parathyroidectomy for secondary hyperparathyroidism. The authors found that 4 of 17 subjects treated with subtotal parathyroidectomy developed recurrent hypercalcemia, and 2 required reexploration. None of the subjects treated by total parathyroidectomy developed recurrent hypercalcemia. Therefore, several authors prefer total parathyroidectomy with autotransplantation.
    - Briefly, parathyroid tissue is cut into approximately 16-20 pieces, each of which measures 1 X 1 mm. These are inserted in pockets in the forearm musculature, and each piece is marked with a polypropylene suture on the fascia. Parathyroid tissue also must be cryopreserved in case the primary autotransplant fails.
- Postoperative details
    - Postoperative care follows the routine described above in <u>Postoperative care</u> for primary hyperparathyroidism.

- o If total parathyroidectomy and autotransplantation are performed, the patient requires a period of maintenance with calcium and calcitriol supplementation.

Outcome and prognosis

Medical treatment of secondary hyperparathyroidism is successful in most patients. Patients who require parathyroidectomy have approximately a 10% risk of recurrent or persistent disease. This may be due to a hyperfunctioning or missed neck gland or hyperplasia of the autograft. Occasionally, a patient has persistent hypoparathyroidism after operation. If tissue has been cryopreserved, transplantation may reverse hypoparathyroidism. If hypoparathyroidism is permanent, lifelong calcium and calcitriol supplementation is necessary.

Tertiary hyperparathyroidism

Tertiary hyperparathyroidism is secondary to long-standing secondary hyperparathyroidism. Tertiary disease is characterized by the development of autonomous hypersecretion of PTH causing hypercalcemia.

Etiology

The etiology is unknown. A change may occur in the set point of the calcium-sensing mechanism to hypercalcemic levels.

Pathophysiology

Tertiary hyperparathyroidism is observed most commonly in patients with chronic secondary hyperparathyroidism and often after renal transplantation. The hypertrophied parathyroid glands fail to return to normal and continue to oversecrete PTH, despite serum calcium levels that are within the reference range or even elevated. In these cases, the hypertrophied glands become autonomic and cause hypercalcemia, even after withdrawal of calcium and calcitriol therapy. This type of tertiary disease is particularly dangerous because the phosphate level is often elevated. If the calcium value multiplied by the phosphate value yields a high product, diffuse calcinosis may occur.

Clinical presentation

The clinical manifestations of tertiary hyperparathyroidism include persistent hyperparathyroidism after renal transplantation or new hypercalcemia in the setting of chronic secondary hyperparathyroidism.

Treatment

Total parathyroidectomy with autotransplantation or subtotal parathyroidectomy is indicated.

Familial benign (hypocalciuric) hypercalcemia

FHH is caused by a loss-of-function mutation of one allele of the gene for the calcium-sensing receptor (*CaR*). It causes hypercalcemia, hypophosphatemia, and hypermagnesemia. The PTH level is usually within the reference range or is mildly elevated. It can be distinguished from primary hyperparathyroidism by low 24-hour urinary calcium excretion. Persons with FHH are asymptomatic. Parathyroidectomy is not indicated.

Hypercalcemia of malignancy

This disorder is usually caused by tumor release of a hormone called PTH-related peptide. Less commonly, hypercalcemia of malignancy is caused by local osteolytic lesions and, rarely, by overproduction of 1,25-dihydroxyvitamin D. This disorder is the most common cause of hypercalcemia in hospitalized patients. The hypercalcemia of malignancy results in a low or undetectable intact PTH level. Usually, it is easily distinguished from hyperparathyroidism. Only a few cases of ectopic production of true PTH are reported in the literature.