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Invited Review

Primary hyperparathyroidism

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ABSTRACT

Primary hyperparathyroidism is a common endocrine disorder caused by overactivation of parathyroid glands resulting in excessive release of parathyroid hormone. The resultant hypercalcemia leads to a myriad of symptoms. Primary hyperparathyroidism may increase a patient's morbidity and even mortality if left untreated. During the last few decades, disease presentation has shifted from the classic presentation of severe bone and kidney manifestations to most patients now being diagnosed on routine labs. Although surgery is the only curative therapy, many advances have been made over the past decades in the diagnosis and the surgical management of primary hyperparathyroidism. The aim of this review is to summarize the characteristics of the disease, the work up, and the treatment options.

Keywords: Primary hyperparathyroidism, parathyroid hormone, parathyroidectomy

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by autonomous production of parathyroid hormone (PTH). Classically characterized as hypercalcemia in the presence of elevated serum PTH concentration , it is now recognized as a spectrum ranging from inappropriately high or even normal PTH in the setting of high-normal or even normal calcium (1). It is the third most common clinical endocrine disorder after diabetes and thyroid disease, with a prevalence between 0.1-1.0% (2, 3) and an incidence of approximately 28 cases per 100,000 individuals in general population (4). The incidence is highest between 50 and 60 years of age, affecting 2% of the population aged 55 years or older, and it occurs 2-3 times more commonly in females (3).

The vast majority of cases (90-95%) are sporadic, in which the PHPT is attributable to a solitary parathyroid adenoma in about 80%-85% of the cases. A double adenoma is present in up to 4% of the cases, and four-gland hyperplasia makes up the remaining 10-15% of the cases (3). Parathyroid carcinoma is a very rare cause of PHPT, accounting for less than 1% of the cases (2). Familial parathyroid disorders are responsible of 5% of the PHPT cases (2), and include such entities as multiple endocrine neoplasia type 1 (MEN 1) and type 2A (MEN 2A), hyperparathyroidism-jaw tumor syndrome, and isolated familial hyperparathyroidism (5). The focus of this review is on non-familial, sporadic PHPT.

The underlying cause for PHPT remains largely unknown, but there are a few known risk factors. Long term use of the drug lithium is associated with an increased risk of PHPT (2). Previous neck irradiation either in the form of external beam radiation or radioactive iodine from previous thyroid ablation is also a risk factor (2, 6). Parathyroid tumors can be due to defects in growth factor genes, proto-oncogenes, or tumor suppressor genes. While sporadic tumors are usually associated with abnormalities in the PRAD1/cyclin D1 genes, familial tumors are due to defects in the RET gene. Both sporadic and familial tumors are associated with HPRT and MEN 1 genes abnormalities (5).

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History

Parathyroid glands were the last organs to be discovered in mammals. In 1850, Sir Richard Owen identified the parathyroid glands in an Indian rhinoceros (7). Thirty years later, a Swedish medical student called Ivar Sandstorm described and actually named the parathyroid glands in humans (7). Between 1908 and 1917, W.G. MacCallum and Carl Voegtlin published a series of studies trying to describe the connection between the parathyroids, calcium, and tetany (7). They also postulated the renal effect of parathyroid secretion. The connection between parathyroid gland's overactivity and bone diseases was established by Schlagenhaufer in 1915 (7). Ten years later, Felix Mandl performed the first parathyroidectomy (conventional bilateral exposure) in a patient with osteitis fibrosa cystica in Vienna (7). The term hyperparathyroidism was first used by Dr. Fuller Albright in 1940s to describe the phenomena of overproduction of PTH (7). In 1963, Berson and Yalow developed an immunoassay for the measurement of parathyroid hormone (8). In 1970s, serum calcium screening test became common practice, which led to increasing numbers of patients diagnosed with PHPT in early stages (8).

Symptoms and Presentation

Currently, the majority of PHPT patients do not present with the classic symptoms of kidney stones or severe bone disease. Individuals are more often diagnosed today through routine biochemical laboratory testing done for other purposes. Although patients often lack the classic symptoms, PHPT is associated with many non-specific complaints such as depression, memory loss, fatigue, sleep problems, bone or muscle pains, gastroesophageal reflux disease, and decreased concentration. In fact, neither patients nor their providers may even recognize these symptoms initially as attributable to the diagnosis of PHPT, but postoperatively, there is often significant improvement resulting in improved quality of life (9-12).

Since calcium homeostasis is important to normal cellular function, the manifestations of PHPT may include musculoskeletal, renal, gastrointestinal, cardiovascular, neuromuscular and neuropsychiatric symptoms (2). A common mnemonic medical students learn about hypercalcemia symptoms is "bones, stones, groans, and psychic moans" (2). The renal manifestations include nephrolithiasis, nephrocalcinosis and hypercalciuria. Since the filtered load of calcium exceeds the reabsorption capacity of the renal tubules, hypercalciuria may occur in about 35-40% of cases (3). Nephrolithiasis can be observed in up to 20% of patients with PHPT (13), but it is becoming a much more infrequent finding at presentation today.

Musculoskeletal manifestations occur from hypercalcemia, but also due to the direct effect of PTH on cortical bones. Parathyroid hormone acts on PTH receptors in osteoblasts, which stimulates osteoblasts differentiation to osteoclasts with subsequent cortical bone resorption (14). Therefore, the persistent high PTH level can lead to osteopenia, osteoporosis, or even to cyst formation and fibrosis. The most severe form of bone disease in PHPT is known as osteitis fibrosa cystica (15). Osteoporosis/osteopenia is by far the most common bone disease associated with PHPT, while osteitis fibrosa cystica is rarely seen in modern clinical practice (3).

In 1988, Joborn et al. (16) stated that 23% of PHPT patients present with neuropsychiatric manifestations, and the majority of them (78%) suffer from depression and anxiety. Recently, the third international workshop held in 2008 reported that presentation of PHPT with psychological and neurological manifestations is common, but the true extent of neuropsychiatric symptoms is still not clear, especially in mild PHPT (9). Many PHPT patients report nonspecific symptoms such as fatigue, mood and sleep disorders, memory loss, irritability, difficulty in concentrating, and loss of initiative. Often, these improve after parathyroidectomy (12), neuropsychiatric manifestations have not yet been considered as one of the indications for parathyroidectomy (9).

In addition to these common symptoms and findings, recent studies have demonstrated that PHPT can affect other organ systems. High PTH levels have been found to have a strong association with several cardiovascular conditions, including valvular and myocardial calcification, arterial hypertension, coronary artery disease, left ventricular hypertrophy, conduction disturbances, and lipid abnormalities (13). Hypercalcemia can also effect the gastrointestinal tract and lead to anorexia, nausea, vomiting, constipation, GERD, and rarely acute pancreatitis (12).

Rarely, PHPT patients may present with parathyroid (hypercalcemic) crisis, which may occur due to significant fluid loss or dehydration leading to rapid rise in blood calcium. During the crisis, patients may experience cardiac and renal function impairment, rapid deterioration of the central nervous system, nausea, vomiting, severe abdominal pain, stomach ulcers, and/or constipation (17).

Diagnosis

The differential diagnosis of hypercalcemia includes: malignancy, PHPT, drugs like lithium and thiazides, vitamins D & A excess, increased oral calcium intake, prolonged immobilization, and medical diseases like milk-alkali syndrome, hyperthyroidism, sarcoidosis, and multiple myeloma (18). While cancer was considered to be the most common cause of hypercalcemia in the inpatient setting, PHPT is the most common cause of hypercalcemia in both outpatient and inpatient settings (19). Hypercalcemia due to PHPT associates with high or inappropriately normal PTH level, whereas other causes of hypercalcemia are usually associated with suppressed PTH levels, because the normal negative feedback mechanism of calcium on the parathyroid glands is intact.

The first step in diagnosing PHPT is collecting a thorough history with particular attention to the symptoms described above. Family history should also be taken to check for the possibility of hereditary forms of PHPT, particularly MEN types 1 and 2A (20). If there is a family history of PHPT, especially in patients younger than 50 years of age, genetic testing for MEN should be considered (20). It is also important to take a detailed drug history from the patients asking specifically about thiazide diuretics, which can raise serum calcium independently of PTH, and lithium, since its long term use is associated with PHPT (20).

The biochemical hallmark of PHPT is hypercalcemia caused by excessive secretion of PTH from one or more parathyroid glands (1). The diagnosis of PHPT is classical when corrected calcium is high in the presence of elevated PTH (20). However, mild PHPT occur when either the PTH or serum calcium level is normal by laboratory definition, but the two values, when considered together, are biochemically abnormal. High PTH in the presence of normal calcium level is called normocalcemic PHPT, and inappropriate secretion of PTH is seen in patients with hypercalcemia and inappropriately normal, or unsuppressed, PTH level (1). Hypercalcemia should cause negative feedback on the parathyroid glands to suppress secretion of PTH, so normal PTH in the setting of high calcium may be an indication of PHPT (Table 1). Different hypothesis have been reported to explain the normocalcemic variety to PHPT. While some surgeons think that this is an early stage of classical PHPT due to an alteration in the regulation of PTH secretion, others believe it is due to the relative resistance to the action of PTH (21).

In patients with normal calcium, but inappropriately high PTH, it is obligatory to rule out secondary hyperparathyroidism (21). Secondary causes of hyperparathyroidism include

Table 1. Primary hyperparathyroidism: clinical presentation

Clinical presentation	Calcium	PTH
Classical primary hyperparathyroidism	High	High
Inappropriate secretion of PTH	High	Normal
Normocalcemic primary hyperparathyroidism	Normal	High

PTH: parathyroid hormone

renal insufficiency, intestinal malabsorption of calcium, and severe vitamin D deficiency (22). Because one action of PTH is the conversion of 25-OH vitamin D to its activated form, low 25-OH vitamin D is often seen in patients with PHPT, but this represents a consequence of excess PTH, not a cause of excess PTH. If a patient has high calcium, high PTH and low 25-OH vitamin D, the patient very likely has PHPT and not vitamin D deficiency. This can be somewhat challenging to sort out in a patient with normal calcium levels (22), however, vitamin D replacement in patients with vitamin D deficiency should normalize PTH while calcium levels remain normal, while vitamin D supplementation in patients with PHPT will drive up serum calcium and not affect PTH. Caution should be used if supplementing vitamin D in patients with suspected PHPT, because this may convert a normocalcemic patient to a hypercalcemic one (22).

Other diagnoses that can present with similar laboratory findings as PHPT include tertiary HPT and familial benign hypocalciuric hypercalcemia (FHH). Tertiary hyperparathyroidism can have the same high calcium and high PTH laboratory findings as PHPT, but it is found in patients with a history of secondary hyperparathyroidism. Secondary hyperparathyroidism converts to tertiary hyperparathyroidism when the physiologic overproduction of PTH in response to low serum calcium converts over to autonomously functioning parathyroid tissue that does not respond to the negative feedback of high calcium. Classically, this is seen in patients with renal failure and secondary hyperparathyroidism who undergo kidney transplant and the parathyroid glands continue to be overactive (2). FHH is an autosomal dominant disease caused by a mutation that inactivates the calcium sensing receptor gene expressed in parathyroid and kidney tissues (23). This perceived lack of calcium by parathyroid cells then causes an increase in PTH secretion that raises serum calcium. It is as if patients with FHH have a higher set point for both calcium and PTH, and these patients are usually asymptomatic young adults with mild hypercalcemia and a positive family history. This may not be a known family history of FHH, per se, but may be something more subtle like having one or more family members who have had failed parathyroid surgery in the past. It is essential to differentiate PHPT from FHH, since surgery is not indicated in FHH, and a 24-hour urine collection for calcium/creatinine clearance ratio should be ordered if there is any suspicion. Low calcium/creatinine clearance ratio (less than 0.01) is highly suggestive of FHH (23).

Imaging

The main aims of preoperative radiological work-up in PHPT are to locate the hyperfunctioning gland or glands and to assess the effect of the disease on end organs. Primary hyperparathyroidism is due to a single, enlarged, adenomatous gland in roughly 80% of patients, and much research in the past 20 years has been dedicated to the question of which patients may be candidates for a targeted approach of that single gland or a more classic identification of all four parathyroid glands and removal of any that are enlarged. Preoperative localization studies should be ordered only if the patient is planned for surgical intervention. Such studies can help the surgeon to decide which surgical approach is best for which patient (20), but it is important to note that negative preoperative parathyroid images do not exclude the diagnosis. Whether or not a patient needs an operation to cure their PHPT is based on laboratory data and history; imaging only serves to guide the type of operation. These preoperative localization studies can be either invasive or non-invasive. Noninvasive methods include neck ultrasound (US), Tc-99m sestamibi imaging, single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), positron emission tomography combined with CT scan (PET/CT), and 4-dimensional CT scan (4-D CT) (Table 2) (24, 25).

Neck US can be used preoperatively as well as intraoperatively just prior to incision to locate the gland and therefore decrease the amount of neck dissection required in the classic four-gland exploration (26). Combined neck US and sestamibi increases the sensitivity and the specificity to more than 90% (27). If both neck US and sestamibi are negative, most surgeons would proceed with an open parathyroidectomy to identify all four glands. Further radiological evaluation at this stage with MRI or 4D-CT scan may reveal ectopic glands (27), but is expensive and in most cases unnecessary as these are patients who will ultimately require a four gland exploration. Magnetic resonance imaging and 4D-CT scan are commonly preserved for reoperative situations where localization is more crucial given the anatomic distortion and scarring from previous surgery (27).

Invasive methods can be employed for reoperative situations and include selective arteriography (60% sensitivity), selective venous sampling (80% sensitivity), and fine needle aspiration (FNA) (24). Selective arteriography depends on the fact that all enlarged parathyroid glands are highly vascular, thus, a contrast can be injected into the inferior and superior thyroid arteries or thyrocervical trunk and can stain the glands. This technique can identify small and ectopic parathyroid glands, but equivocal findings occur in 10-15% of cases due to intrathyroidal parathyroid adenoma or thyroid nodules (25). Arteriography is often combined with venous sampling for more accurate results. Extensive sampling of the thyroid venous plexus and thymic veins is needed. This technique is helpful to differentiate between adenoma and hyperplasia because adenomas produce unilateral hypersecretion of PTH whereas hyperplasia exhibits elevated PTH throughout the venous plexus bilaterally (25). The invasive methods carry a higher risk of complications, such as embolism, stroke and renal impairment (24).

A focus of tissue that is seen on imaging that is suspicious for parathyroid tissue may be sampled by FNA, and then the aspirate can be tested for PTH level. FNA of suspicious parathyroid adenomas for definitive diagnosis is not necessary in most situations, but can be quite useful in reoperative situations or in situations where the area of suspicion is unusual

Table 2. Localization imaging studies

Image name and type	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
Tc Sestamibi Functional	75-90	75-98	- Standard preoperative localizing test - Minimal radiation - For radioguided parathyroidectomy - Excellent anatomical localization if combined with SPECT	- Limited sensitivity in multiglandular diseases - Takes a long time for the patient (2-4 hours), inconvenient - Cannot reliably distinguish thyroid nodule from parathyroid glands
US Anatomical	70-80	80-89	- Cheap, non-invasive, quick, portable - No radiation or IV contrast - Can be done preoperatively and intraoperatively	- Operator dependent - Poor sensitivity in detecting substernal, retroesophageal and retrotracheal parathyroid glands - Cannot detect small lesions <5mm
CT/4D CT				
Anatomical/ Functional	50-80	80-98	- More sensitive than ultrasound for smaller lesions - Allows for visualization of mediastinum	- Radiation exposure and risks of IV contrast - Cannot differentiate parathyroid tissue from other types of tissue like lymph nodes
MRI				
Anatomical	65-80	88-95	- Avoids radiation and IV contrast	- Limited availability - Limited use due to claustrophobia

Tc Sestamibi: technetium sestamibi; SPECT: single-photon emission computerized tomography; US: ultrasound; IV: intravenous; CT: computerized tomography; 4D CT: 4 dimensions computerized tomography; MRI: magnetic resonance imaging

for parathyroid, such as intrathyroidal or lateral to the carotid artery. There is a controversy regarding the cutoff point for a positive test of PTH aspirate from FNA. Frasoldati and colleagues reported that a PTH washout value of more than 101 pg/mL had a 100% specificity and sensitivity for confirmation of parathyroid tissue (28). Furthermore, Maser and colleagues regarded a PTH washout value of >1,000 pg/mL as positive for sampling parathyroid tissue (29). In 2013, Abdelghani and his colleagues stated that due to the hormone dilution in the FNA, a PTH washout value greater than the serum PTH should be considered diagnostic in localizing the parathyroid (30). Although parathyroid sampling can be done using FNA, Conrad et al showed that 1 mm^3 biopsy with PTH cutoff of 1000 pg/dl is more accurate and more sensitive than FNA (4).

Regarding end–organ assessment in PHPT, renal US, abdominal plain film, or CT scan could be done to rule out nephrolithiasis or nephrocalcinosis if there is any renal complaint, as these are findings that would argue for surgical intervention (13). Moreover, bone mineral density using dual energy X-ray absorptiometry of the lumbar spine, femur, and distal 1/3 radius should be done in all patients with PHPT to assess the extent of skeletal bone involvement (13). Finally, if patients have specific skeletal complaints, targeted plain film X-rays may reveal subperiosteal resorption of the middle and distal phalanges, a mottled or " salt and pepper " skull pattern, thinning of the distal clavicles, or bone cysts and brown tumors in the long bones and pelvis, though these are found in severe cases that are rarely seen today (3).

Treatment

Surgical treatment

Surgery is the only curative therapy for PHPT. Currently, surgery is recommended for all symptomatic PHPT patients. Recent consensus guidelines recommend surgery for asymptomatic PHPT patients under the age of 50, with evidence of osteoporosis or vertebral fracture, with a calcium higher than 1 mg above the upper limits of normal, a creatinine clearance of <60 cc/min, or presence of nephrolithiasis or nephrocalcinosis in radiological images (Table 3) (31). Inability to participate in adequate follow up is also considered one of the criteria (31).

Furthermore, asymptomatic PHPT cases who have worsening laboratory values or cortical bone loss on follow up should be considered for surgery, according to the consensus response to the International Task Force on PHPT proceeding the third international workshop (9).

Outside of the consensus guidelines, several researches demonstrated that medical follow up is time-consuming and expensive (26), while parathyroidectomy is cost-effective compared to observation in treating both symptomatic and asymptomatic PHPT patients with a life expectancy of more than 6.5 years (32). Risk of surgery is low, and continues to improve especially in the hands of experienced, high-volume endocrine surgeons (33). Because of these considerations, and also because we now recognize a host of symptoms that improve with parathyroidectomy, many authors advocate operating on patients with milder disease before consensus guideline criteria are met (26, 32-34).

The two main operative approaches are bilateral neck exploration and minimally invasive parathyroidectomy (MIP). The classic bilateral neck exploration was the standard surgical treatment for PHPT up until about the last 15 years. In this approach, the surgeon identifies and inspects all 4 glands with subsequent removal of enlarged and presumed to be

Table 3. A comparison of Guidelines for Parathyroidectomy in Asymptomatic PHPT patients

Clinical factor	1990	2002	2008	2013
Age	<50 years	<50 years	<50 years	<50 years
Serum calcium	>1.6 mg/dL above normal	>1 mg/dL above normal	>1 mg/dL above normal	>1 mg/dL above normal
Renal function	CrCl decreased by >30%	CrCl decreased by >30%	Estimated GFR <60 mL/min/1.73 m^2	CrCl <60 cc/min, increased stone risk by biochemical stone risk analysis, or presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT scan
BMD	Z-score <-2 at forearm	T-score <-2.5 at hip, lumbar spine, or distal radius	T-score <-2.5 at any site or previous fragility fracture	T-score <-2.5 at lumbar spine, total hip, femoral neck, or distal radius, or vertebral fracture
Urine calcium	>400 mg/24 h	>400 mg/24 h	Not included as a criterion	>400 mg/24 h

PHPT: primary hyperparathyroidism; CrCl: creatinine clearance; GFR: glomerular filtration rate; CT scan: computerized tomography scan; BMD: bone marrow densitometry

hyperfunctioning gland(s). The success rate for this approach is over 95% (2).

Over 80% of PHPT is due to a single adenoma, and imaging techniques are ever improving at being able to identify a single enlarged gland. Additionally, the introductions of intraoperative PTH (ioPTH) monitoring in 1988 and radioguided operative techniques in 1997 (35, 36) have contributed to the trend that focused, or MIP, has replaced the conventional bilateral exploration in many cases.

Minimally invasive parathyroidectomy approach focuses on a targeted, unilateral neck exploration with removal of the hyperfunctioning adenoma (26). This approach relies on preoperative and intraoperative localization techniques (11). Currently, there are several perioperative adjuncts that can facilitate the MIP approach and increase its success rate (Table 4) (26, 29, 30, 37-39). The most important adjunct is the ioPTH monitoring, which is an important tool used in MIP to predict operative success. Different criteria have been proposed for determination of operative cure using ioPTH, and each has different sensitivity for predicting cure and detecting multiglandular disease. The most common criteria for ioPTH assay are: Halle, Miami, Rome, Vienna, and Wisconsin criteria (Table 5) (37). In 2009, Barczynski et al. (37) evaluated these different criteria except Wisconsin criterion in predicting cure and multiglandular disease and concluded that Miami criterion followed by Vienna criterion were the best in predicting cure, while Rome criterion followed by Halle criterion are the most useful ones in detecting multiglandular disease.

Minimally invasive parathyroidectomy was compared to bilateral exploration in several prospective, well-designed studies that showed MIP has similar cure and postoperative complication rates when performed by experienced surgeons. Furthermore, it has shorter operative time, less postoperative pain, and greater cosmetic satisfaction (40). However, MIP is associated with a slightly higher recurrence rate (40). Conversion from MIP to bilateral exploration usually takes place when ioPTH criteria are not met, localization is incorrect, or there is a concern for multiglandular disease intraoperatively (41). The experience of the operating surgeon is considered to be the most important single factor to predict cure rate.

Complications

After parathyroidectomy, there are some complications that can occur regardless of the type of surgery. These complications include hematoma formation leading to airway obstruction, hypoparathyroidism/hypocalcemia, recurrent laryngeal nerve injury, and failure to cure hyperparathyroidism (11). Recurrent laryngeal nerve injury, which can be transient (<6 months) or permanent (>6 months), unilateral or bilateral, is rare (less than 1%) especially in expert hands (26), but can lead to voice changes, aspiration, or even airway obstruction in cases of bilateral injury. Hypocalcemia is seen more frequently, especially transient hypocalcemia, which can occur in up to 30% of patients after surgery (42). Normally, this can be managed with oral calcium supplementation with or without activated vitamin D. Patients with severe hypercalcemia and very high preoperative PTH levels are at higher risk for transient hypoparathyroidism, as post-parathyridectomy transient hypocalcemia can be due to suppression of the remaining parathyroid glands, devascularization, hungry bone syndrome (which is an immediate uptake of calcium by the bone after successful parathyroidectomy that results in severe hypocalcemia), or to a lesser extent due to hypomagnesemia (42). Permanent hypocalcemia is due to removal or devascularization of all functioning parathyroid tissue and is thankfully rare (1-2%).

Benefits of Parathyroidectomy

Parathyroidectomy is the only definitive therapy for PHPT. It may correct the biochemical abnormality, improve the quality of life, improve BMD, and decrease the risk of fractures (26). Improvement in BMD postparathyroidectomy in both symptomatic and asymptomatic patients has been reported by both observational studies and clinical trials (13). Previous studies suggested that parathyroidectomy reduces the risk of fracture in PHPT patients (26). In addition, parathyroidectomy can reduce the risk of nephrolithiasis. Silverberg et al. (43) reported that the recurrence rate of renal stones is 75% in patients treated conservatively, while it is 0% in patients treated surgically. Furthermore, neuropsychiatric manifes-

Table 4. Perioperative adjuncts

Adjuncts	Description	Positive test	Comment
Intraoperative PTH (ioPTH)	- Peripheral blood sample is drawn prior to skin incision (baseline). - Other samples are drawn 5, 10, 15 min after resection of the hyperfunctioning gland (26)	≥50% drop from baseline at 10 min post-resection (36) (please see table 5)	- Useful when preoperative localization imaging are discordant 36) - Useful in re-operative parathyroidectomy - Positive test indicates surgical cure (26)
RGP	- Patients receive an intravenous dose of ^{99m}Tc-sestamibi 1-4 h prior to surgery (26) - In O.R., a gamma probe is placed over the thyroid isthmus to measure the background level of radioactivity then over the suspected parathyroid gland (26)	>20% of background count (37)	- It can be used to optimize the incision location and to direct the actual dissection (26) - Can distinguish between thyroid nodules and parathyroid tissue (26) - Can localize ectopic parathyroid glands (37)
BIJ VS	- Direct (intraoperative) or indirect (preoperatively) sampling is obtained from both right and left internal jugular veins (38)	5-10% difference between right and left IJ veins samples (26, 38)	- Particularly useful for localization of hypersecreting glands in multiglandular disease cases where ioPTH levels did not fall by 50% after removal of one abnormal gland (26)
FS / FNA	- A biopsy or an aspirate is taken from the suspected gland	PTH in the aspirate >1000 pg/mL (29) or > serum PTH level (30)	- Useful to differentiate parathyroid tissue from others (lymph node, thyroid) particularly in re-operative cases (29, 30)

RGP: radioguided parathyroidectomy; Tc-sestamibi: technetium sestamibi scan; IJ vein: internal jugular vein; FS: frozen section; FNA: fine needle aspiration; PTH: parathyroid hormone

tations such as cognition, mood, and anxiety may improve after parathyroidectomy (26). Some studies demonstrated that parathyroidectomy has cardiovascular benefits such as improvement of the left ventricular diastolic function, the blood pressure, and left ventricular mass index, while other studies failed to confirm these findings (26). The majority of the current data is from observational studies that have several limitations, such as selection bias (10, 26). Well designed long-term randomized studies are needed to define the actual benefits of parathyroidectomy for each manifestation (44).

Follow up

Cure is defined as normocalcemia 6 months after resection (26). Thus, patients should be evaluated in the clinic for serum calcium 1-2 weeks postoperatively and then 6 months after resection. If normal, the patient should be followed by checking the calcium level annually (26). Since we are now operating on milder forms of PHPT, including those patients with normocalcemic hyperparathyroidism, one may question whether normal serum calcium levels after surgery is an adequate measure of cure. Normocalcemia with high PTH level can be detected in up to 40% of patients post-parathyroidectomy and may not indicate operative failure (45). The significance of elevated PTH postoperatively is not yet fully understood. High postoperative PTH level can be due to vitamin D deficiency, hungry bone syndrome, inadequate calcium intake, vitamin D end-organ resistance, renal insufficiency with impaired vitamin D production, or the use of loop diuretics such as furosemide that increase calcium excretion (45). Interestingly, Ning et al. (46) demonstrated that recurrent disease is significantly more common in patients with postoperative high PTH and it was always associated with a serum calcium level ≥9.7 mg/dL. Moreover, Ning et al. (46) and Oltmann et al. (45) recommended early postoperative PTH level measurement to detect such patients in the early stages. If PTH is high on the first check, the surgeon should replete vitamin D and check PTH level again in a month to six weeks.

Persistent and Recurrent PHPT

Approximately 2-5% of PHPT patients who undergo parathyroidectomy will need further surgical intervention for either persistent or recurrent disease (26, 47). Persistent PHPT is defined as hypercalcemia within 6 months of parathyroidectomy and it occurs in about 3.9% (48). It is likely due to failure to identify and remove all hyperfunctioning glands. Recurrent PHPT can occur in 2-3% of cases (40) and it is defined as hypercalcemia that occurs six months after parathyroidectomy, provided that the patient has been eucalcemic during the first six months after resection. It is thought to be due to regrowth of abnormal parathyroid tissue (26).

Once the diagnosis is established, all the preoperative images, final pathology report, and operative report should be reviewed carefully (26). The first line of investigation is to use noninvasive preoperative localization studies, like neck US, sestamibi scan, MRI or 4-D CT scan. If noninvasive studies failed to localize the diseased gland(s), invasive techniques such as venous sampling for PTH levels may be used (48). Intraoperative adjuncts like US, ioPTH monitoring, and radioguided parathyroidectomy are recommended in reoperative parathyroidectomy. The cure rate for reoperative parathyroidectomy for PHPT ranges from 76% to 94% (48). However, the complication rate of reoperative parathyroidectomy is higher, in which up to 13% of patients may develop permanent hypoparathyroidism, and up to 4% may suffer from recurrent laryngeal nerve injury (49).

Medical Treatment

The medical treatment is an alternative therapy for those patients who cannot undergo surgical intervention. The aims

Table 5. Intra-operative parathyroid hormone criteria

	Baseline sample	5 min post-excision	10 min post- excision	15 min post-excision	20 min post-excision	Definition of surgical cure
Wisconsin	Pre-incision	*	*	*	**	- >50% drop from the baseline at 5, 10, or 15 min post-excision - If 5 minute PTH > baseline PTH, 5 min PTH level becomes "new baseline" and another sample is drawn at 20 min
Halle	Pre-operative			*		- Intraoperative PTH ≤35 pg/mL at 15 min post-excision
Vienna	Pre-incision		*			- ≥50% drop at 10 min post-excision
Miami	Pre-incision and pre-excision		*			- ≥50% drop at 10 min post-excision from the higher baseline
Rome	Pre-incision and pre-excision		*	*	*	- ≥50% drop at 10 min post-excision from the higher baseline and/or - Intraoperative PTH in the reference range at 20 min post-excision and/or - Intraoperative PTH level at 15 or 20 min post-excision is ≤7.5 pg/mL lower than the value at 10 min post-excision

*Intraoperative parathyroid hormone sample(s), **drawn only if 5 minutes level is higher than the baseline, IoPTH: intraoperative parathyroid hormone; PTH: parathyroid hormone

of medical management are either to balance calcium homeostasis by using calcimimetic drugs such as cinacalcet, or to improve the bone mineral density by using antiresorptive drugs (11), which include estrogen, selective estrogen receptor modulators, and bisphosphonate (13, 26). Medical management of PHPT is indicated in the following conditions: patients who are unfit for or refuse surgery, pregnant women in the first or the third trimester, patients who are waiting for surgery, and patients with failed surgical treatment (50).

Medical treatment has been shown to stabilize the disease over a period of ten years, however, over a period of 15 years, laboratory values and/or cortical bone loss may worsen in up to 37% of cases (26). Because there is no way to predict which patient will progress, medically managed patients should be monitored with calcium level and renal function annually, and DEXA scan every 1-2 years (31). They are advised to avoid factors aggravating hypercalcemia such as drugs (thiazide diuretics and lithium), immobilization, dehydration, and high dietary calcium (51).

CONCLUSION

Primary hyperparathyroidism is the most common cause of hypercalcemia in the outpatient population. Currently, it is often diagnosed in the Western world at an asymptomatic stage. Classical symptoms are due to the affect of hypercalcemia or high PTH level on body systems specifically bone, kidney, and central nervous system. Other nonspecific symptoms include weakness, malaise, fatigue, and mood disturbances. The diagnosis of PHPT is confirmed in the presence of hypercalcemia and an inappropriately normal or elevated PTH level in the absence of conditions that mimic PHPT. Indications for surgery have recently been revised based on international consensus, and surgery is advised in the presence of significant hypercalcemia, impaired renal function, and osteoporosis and in individuals younger than 50 years. The classical complications of PHPT are skeletal fragility, nephrolithiasis, and nephrocalcinosis. Surgery is always appropriate in an individual with confirmed PHPT after excluding conditions that can mimic PHPT and in the absence of contraindications. Individuals with asymptomatic PHPT with contraindications for surgery may be followed and considered for medical management.

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