REVIEW ARTICLE

The Panorama of Hyperparathyroidism

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Abstract

Hyperparathyroidism occurs due to increased production of the parathyroid hormone (PTH) from the parathyroid glands. This can stem from abnormal secretion of the hormone as seen in primary and tertiary hyperparathyroidism. It can also be caused by defective homeostasis of the calcium metabolism, which can stimulate the production of PTH as in secondary hyperparathyroidism. The third most common endocrine disorder is primary hyperparathyroidism (PHPT), with its incidence being the highest among postmenopausal women. Seventy to eighty percent are asymptomatic, and the symptoms are related to chronic hypercalcemia rather than the elevated hormone levels. In the symptomatic group, nephrolithiasis is the most common followed by osteoporosis and increased fracture risk. With the advent of new diagnostic modalities, the severe presentation of the disease has decreased. Surgical excision of the gland(s) is a modality of choice for PHPT. Medical management is done using bisphosphonates, hormone replacement therapy, and calcimimetics and is usually required for mild disease. Secondary hyperparathyroidism occurs when the body tries to compensate for the low levels of ionized calcium by overproduction of the hormone. In the older population, vitamin D deficiency is a common cause of secondary hyperparathyroidism. Another cause is chronic kidney disease (CKD); these patients present with bone disease termed as osteodystrophy. It is also associated with cardiovascular disease and increased mortality. Treatment of secondary hyperparathyroidism is primarily medical using vitamin D supplements and calcium-based phosphate binders and calcimimetics. Dialysis is used for the management of acute nature. Tertiary hyperparathyroidism is usually a result of long-standing secondary hyperparathyroidism with autonomous parathyroid production. It can also occur with a few genetic diseases. Total parathyroid gland removal with autotransplantation in the forearm is the preferred management.

Keywords: Hypercalcemia, Hyperparathyroidism, Primary hyperparathyroidism.

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Introduction

The parathyroid hormone is the primary regulator of calcium physiology and is produced by the parathyroid glands located posterior to the thyroid gland. Regulation of ionized calcium is regulated closely to maintain the range between 1.1 and 1.3 mmol/L.[1] This meticulous control is essential for the optimal physiological functions from cytoplasmic to the tissue level such as cell signaling, neuronal functions, muscular activity, and bone metabolism. Parathyroid hormone plays a central role by responding to changes in the ionized calcium concentrations via the receptor on the chief cells called the calcium-sensing receptor (CaSR).[2] Parathyroid hormone increases the ionized calcium concentration in the plasma by three major mechanisms, increasing the tubular reabsorption in the kidneys, stimulation of bone resorption, and upregulating the activity of renal alpha 1 hydroxylase to increase production of 1,25 dihydroxy vitamin D, which increases absorption of calcium from the bowel. Thus, the net effect is on bone, gut, and kidney to increase the serum calcium, which acts as feedback and inhibits the release of PTH (Flowchart 1). There is another action of PTH on the renal tubules that it inhibits the reabsorption of phosphate ions in both proximal and the distal tubules leading to the movement of phosphate ions from bone to blood to urine. Defects in any component of these meticulously operating feedback loops can lead to increased secretion of PTH, which is also known as hyperparathyroidism.

Based on the underlying pathology, hyperparathyroidism can be classified into three types, primary, secondary, and tertiary. Primary hyperparathyroidism occurs when one or more parathyroid glands secrete the PTH hormone because of abnormal change intrinsic to the gland. Secondary hyperparathyroidism is when there is a defect in the kidney, liver, or bowel, which causes lowered serum calcium and in turn increased production of PTH. This is an extrinsic abnormal change affecting calcium homeostasis. Tertiary hyperparathyroidism is an intrinsic abnormality, in which there is an autonomous secretion of the hormone, because of long-standing CKD.

These three entities, although characterized by raised PTH levels, are completely different disorders. The pathology, etiology, epidemiology, clinical presentation, and management vary vastly. The primary aim of this review is to discuss in detail their clinical presentation and health effects.

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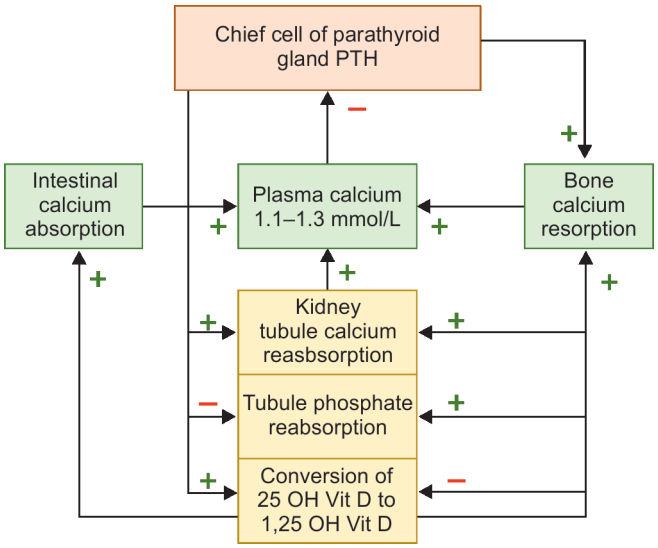
Primary Hyperparathyroidism

The description of PHPT dates back to approximately 90 years ago.[3] When it was described as a severely symptomatic disease with the characteristic "stones, bones, abdominal groans, and psychic moans".[4] However, now it has transformed into more of

Flowchart 1: Physiological control of calcium homeostasis with feedback loops involving the parathyroid gland and the three target organs, bone, kidney, and bowel



an asymptomatic disease with incidental diagnosis. It should be viewed as a generalized disorder of calcium, phosphate, and bone metabolism caused by elevated PTH.

Epidemiology and Etiology

Primary hyperparathyroidism is a relatively common problem, with earlier incidence rates of approximate 22 cases per 100,000 persons per year.[5] However, the incidence varies from 0.4 to 82 cases per 100,000.[6,7] Females account for about three fourths of all cases but the incidence rates are similar in men and women before age 45 years. Primary hyperparathyroidism peaks in the seventh decade of life.[8] In about 80% of the cases, the raised PTH can be attributed to a single gland adenoma. Another 10–15% can be explained by four-gland hyperplasia and about 5% with more than one gland adenoma. Parathyroid carcinoma accounts for <1% of cases of PHPT. The underlying cause in sporadic cases of PHPT is unknown. Risk factors such as exposure to ionizing radiation and chronic lithium use have been established.[9,10] Whereas, in the inherited forms of PHPT, various genes and syndromes have been identified.[11,12] Their clinical features, inheritance, and pathogenic mechanism are discussed in Table 1.

Clinical Manifestation and Pathophysiology

The basic feedback loop of calcium homeostasis is altered in PHPT with loss of suppression of PTH release by raised serum ionized calcium. This occurs either due to increased chief cell mass or reduced expression of CaSR proteins on the chief cells in the parathyroid gland.[13] This, in turn, leads to a higher level of serum ionized calcium to suppress the PTH secretion, as depicted in Figure 1 with the shift of the curve toward the right side. The presentation can be broadly divided into the classical PHPT with the textbook symptoms and the other end being the asymptomatic PHPT. The incidence of which is increasing with advances in diagnostic modalities.

Classical PHPT

This was the clinical picture presented in the era before 1970s when the routine measurement of serum calcium was not done. It is a symptomatic multisystem disorder with involvement of kidneys, skeletal, and gastrointestinal systems with neuropsychiatric abnormalities and increased mortality.[3] The symptomatic profile included raised serum calcium (11.5–16.8 mg/dL), osteitis fibrosa cystica, characterized by bone pain, vertebral fractures, fibrosis and brown tumors with radiographical decreased bone mineral density which is referred to as salt and pepper appearance of the skull.[3,14] Renal manifestations included polyuria, polydipsia, renal stones, nephrocalcinosis, and ultimately renal function impairment. Gastrointestinal symptoms are characterized by abdominal pain caused by either the peptic ulcer disease or pancreatitis. Constipation, anorexia and muscle weakness, and type II fiber atrophy are also seen. Neuropsychiatric complaints include mental disturbances, fatigue, and lassitude.[3,14] This classical PHPT is now rarely seen in the Western countries with the USA having rates of renal stones to be <20 and <2% of patients having osteitis fibrosa cystica.[15,16] However, the classical presentation is seen more in countries with an endemic deficiency of vitamin D and resource-poor counties lacking the routine serum calcium screening. Classical variant still remains the predominant phenotype in Middle East, Asia, South Africa, and India.[17–20] The following subsections will deal with each systemic involvement as seen in the modern PHPT, which, like most things in life, lies somewhere in the middle of classical and asymptomatic PHPT. The manifestations are summarized in Table 2.

Skeletal system involvement: The skeletal manifestations range from the overt osteitis fibrosa cystica to subclinical decreased bone mineral density (BMD). The variant of classic PHPT with predominant skeletal symptoms is eponymously known as von Recklinghausen's disease. Prevalence of osteoporosis in PHPT is estimated between 39% and 63% by various studies.[21–23] This should be taken with a pinch of salt as the existence of osteoporosis would have led to screening for PHPT. However, mean T scores on dual-energy X-ray absorptiometry (DXA) scan lie in the osteopenic range for the majority of patients.[21,22] The PTH has a differential catabolic and anabolic effect on different skeletal components with preferential loss of BMD in cortical bones such as limb bones, iliac crest, and sparing of cancellous sites such as the lumbar spine.[24,25] This should have been extrapolated as an increased risk of peripheral fractures and reduced vertebral fractures in patients with PHPT. On the contrary, the data suggest an increased risk of both vertebral and peripheral fractures.[26–29] This paradox was not explained until now when a non-invasive method was used to assess the microarchitecture of the bone by the high-resolution peripheral quantitative CT (HRpQCT) and the trabecular bone score. This demonstrated that there was trabecular deterioration in cortical as well as cancellous sites.[30–32] The risk factors for fractures in PHPT remain the same as the ones in the general population, such as the advanced age, less body weight, less bone density, vitamin D deficiency, raised PTH levels, and high-level markers of bone turnover. Trabecular distortion has not proven to be a risk factor.[23,33] All patients with asymptomatic PHPT should be screened for silent vertebral fractures and their presence warrant a surgical removal of the pathological gland(s). Likewise, parathyroidectomy reduces the risk of vertebral fracture in asymptomatic cases.[23,34]

Table 1: Genetic syndrome associated with PHPT[11,12]

Inherited disorder	*Associated gene(s)*	*Inheritance*	*Pathogenic mechanism*	*Associated clinical features*	*Mean age of PHPT (years)*	*Surgical approach*
MEN 1	*MEN1* (menin)	Autosomal dominant	Loss of function mutation	PHPT (95%), anterior pituitary adenomas (30%), pancreatic neuroendocrine tumors (40%); other features can include adrenal adenomas, carcinoid, lipomas, angiofibromas and collagenomas	25–45	Subtotal Parathyroidectomy with thymectomy
MEN 2A	*RET* (c-RET)	Autosomal dominant	Gain of function mutation	Medullary thyroid cancer (90%), pheochromocytoma (50%), PHPT (20%)	38	Removal of abnormal parathyroid gland after ruling out pheochromocytoma
MEN 4	*CDKN1B* (p27)	Autosomal dominant	Loss of function mutation	PHPT (80%), anterior pituitary tumors (40%), pancreatic neuroendocrine tumors; other features can include carcinoid, adrenocorticoid tumors, thyroid tumors, reproductive organ tumors and renal angiomyolipomas	50	Subtotal parathyroidectomy with thymectomy
Familial isolated hyperparathyroidism	*MEN1* *CaSR* *GCM2* *CDKN1B*	Autosomal dominant	Loss of function mutation	Isolated PHPT	39	Bilateral neck exploration with removal of abnormal glands. En bloc resection of parathyroid carcinoma
Hyperparathyroid–jaw tumor syndrome	*CDC73 (HRPT2/ Parafibromin)*	Autosomal dominant	Loss of function mutation	PHPT (80%), often parathyroid carcinoma (>15%), jaw tumors (>30%); other features can include renal abnormalities, uterine tumors, pancreatic adenocarcinoma, testicular mixed germ cells and Hürthle cell thyroid adenomas	32	Bilateral neck exploration with intraoperative PTH. En bloc resection of parathyroid carcinoma
Familial hypocalciuric hypercalcemia	*CaSR*	Autosomal dominant	Loss of function mutation	Rare pancreatitis, relative hypocalciuria (24-hour urinary calcium:creatinine ratio, <0.01)	20s	No role of surgical intervention
Neonatal severe primary hyperparathyroidism	*CaSR*	Autosomal dominant	Loss of function mutation	Life-threatening condition with marked hypercalcemia, hypotonia, and respiratory distress	Neonate	No role of surgical intervention

CaSR, calcium-sensing receptor; PHPT, primary hyperparathyroidism

Renal involvement: Symptomatic renal stone disease is present in about 10–20% of cases.[15,35] The risk factors for the same include male sex and younger age. Other factors with the low association are PTH levels, serum ionized calcium levels, and level of hypercalciuria.[35–38] Screening for nephrolithiasis should be done while managing asymptomatic PHPT.[23,34] Features that are seen uncommonly now are nephrocalcinosis that is, diffuse deposition of calcium–phosphate complexes in the parenchyma, polyuria, and polydipsia.[35] In addition to nephrolithiasis and nephrocalcinosis, PHPT is associated with obesity, glucose intolerance, and hypertension. All of these factors combined can cause renal function impairment.[39,40] Renal impairment is defined as estimated glomerular filtration rate (eGFR) <60 mL/minute. The prevalence of renal impairment is estimated to be 15–17%, and in longitudinal studies, the renal function remains stable in cases of PHPT.[40–42] The impairment has shown no improvement with parathyroidectomy.[42–44]

Neuropsychiatric involvement: The classical description of neuropsychiatric symptoms included mental fuzziness, fatigue, depressed mood, headache, and transient paralysis resembling cerebrovascular event.[3] The pathogenesis of these manifestations can be explained by the fact that calcium has a key role in neurotransmitter release at synaptic junctions and increased ionized calcium can hamper the process. Parathyroid hormone also has been shown to alter cognition, mood, and cerebrovascular perfusion.[45–47] However, the exact mechanism is still unknown. The modern forms of PHPT do not have muscle weakness. They typically comprise symptoms such as anxiety, depression, fatigue, sleep cycle alteration, and cognitive disorder. These all-combined lead to a decrease in quality of life. Whether or not these symptoms improve with parathyroidectomy is not proven beyond doubt with randomized control trials resulting in mixed results.[43,44,48] The guidelines do not recommend removal of glands solely for neuropsychiatric symptoms.[34]

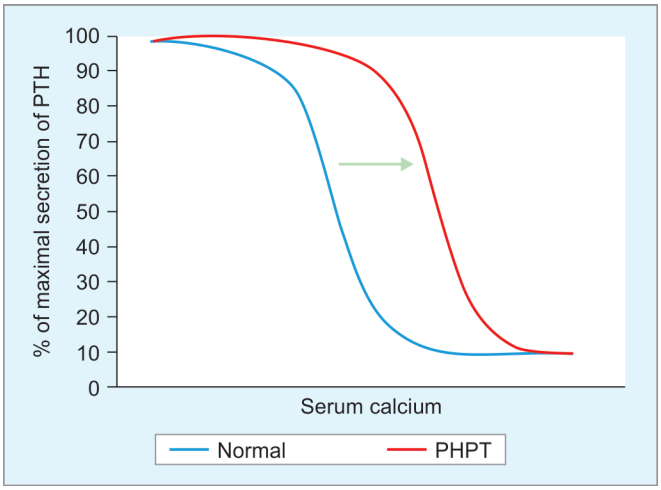


Fig. 1: Relationship between serum calcium and PTH in normal individuals (blue) and in PHPT (red) with a shift to right. Higher level of serum calcium is needed to inhibit the PTH release

Table 2: System-wise manifestations of PHPT

System involved	*Manifestations*
Renal	• Nephrolithiasis • Nephrocalcinosis • Polyuria • Polydipsia • Renal insufficiency
Skeletal	• Fragility fractures • Osteopenia/osteoporosis • Bone pain • Osteitis fibrosa cystica
Neuropsychiatric	• Fatigue • Anxiety • Emotional lability • Sleep disturbances • Lethargy • Memory loss • Psychosis • Obtundation • Coma
Neuromuscular	• Proximal muscle weakness • Muscular atrophy • Gait disturbance • Easy fatigability • Generalized weakness
Cardiovascular	• Exacerbation of hypertension • Valvular disease • Myocardial calcifications • Premature atherosclerosis • Left ventricular hypertrophy • Shortened QT interval • Conduction abnormalities • Heart block
Gastrointestinal	• Gastroesophageal reflux • Constipation • Abdominal pain • Peptic ulcer disease

Cardiovascular involvement: The pathophysiology of cardiovascular involvement is not entirely elucidated in the literature. There are conflicting data on increased intima and media thickness in the vessel wall.[47,49,50] Some studies have even demonstrated the association of vascular stiffness with PTH levels; however, they are consistently irreversible on parathyroidectomy.[51–53] Clinically, the association of hypertension and PHPT is long and old one.[54] Recently, a lot of studies have shed a light on the subclinical cardiovascular manifestations present in PHPT. These are valve calcification, which is present in a greater area as compared to individuals without PHPT and mild PHPT.[55,56] Other features such as coronary artery disease and left ventricular hypertrophy have been associated with PHPT, but they are most likely attributed to the traditional risk factors rather than the disease.[54,57–59] Asymptomatic to mild PHPT did show any increase in mortality due to cardiovascular causes, but moderate to severe PHPT has shown increased mortality.[54,60] Thus, due lack of unequivocal data, parathyroidectomy is not recommended for isolated cardiovascular involvement.[34]

Gastrointestinal involvement: The classical description of acute pancreatitis and peptic ulcer disease is seldom seen in the modern PHPT. Constipation is however a common complaint, whether attributed to PHPT is debatable.[61,62] The individuals with celiac disease have a long-standing deficiency of vitamin D so are at risk of developing PHPT.[63]

Asymptomatic PHPT

It was introduced in 1970s to differentiate the individuals without the classical symptoms. And it is defined as PHPT without renal or skeletal involvement. However, over the years this term has evolved as an umbrella to include mildly symptomatic individuals to those diagnosed incidentally due to the biochemical profile. The typical biochemical abnormality is hypercalcemia with increased PTH levels up to twice the upper limit of normal. Serum phosphate levels are either at the lower limit of normal or decreased. Alkaline phosphatase (ALP) can be elevated because of bone resorption but can be within the normal limits, depending upon the compensatory change. The storage form of vitamin D, 25 hydroxy Vitamin D is decreased, whereas, the active form, 1,25 dihydroxy vitamin D is within the normal range or elevated. This is because of the upregulation of the 1-alpha hydroxylase enzyme in the renal parenchyma by the PTH hormone. Individuals with vitamin D deficiency have increased serum calcium levels, lower phosphate levels, and higher ALP levels, indicating a severe form of the disease. Thus, Vitamin D deficiency is a risk factor for a severe form of PHPT.[64,65] There has been an evolution in the biochemical profile of the individuals with PHPT over the years, marked by increased levels of 25 hydroxy vitamin D and lower values of PTH. These are explained by self-supplementation of Vitamin D supplements, available over the counter.[66]

Normocalcemic PHPT

Normocalcemic PHPT (NPHPT) is a phenotype of PHPT with normal serum calcium levels. It has a prevalence of 0.4–3.1%.[67] The clinical manifestation of NPHPT has high rates of nephrolithiasis, osteoporosis, and bony fractures.[68–70] This is against the general perception that NPHPT will have a milder form of the disease, one explanation comes from selection bias present in the study, as the attention to the patient is only drawn when symptoms appear. Bone mineral density in these individuals is similar to controls and there are no reports of neuropsychiatric

or gastrointestinal symptoms. However, more clinical studies need to be conducted to delineate the detailed symptomatic profile of this phenotype.

Biochemically, it is characterized by normal calcium levels, lower levels of PTH as compared to hypercalcemic PHPT.[68,71] Higher phosphate levels and lower levels of 1,25 dihydroxy Vitamin D. To differentiate this entity from secondary hyperparathyroidism, ionized calcium, vitamin D, urinary calcium level and kidney function must be normal.[68] Natural history of NPHPT is variable, it can lead to the development of hypercalcemic PHPT in 0.6–19% cases. Individuals with a higher level of calcium (within the normal range) and higher hypercalciuria levels are at risk of this progression.[67,68,72]

Differential Diagnosis

The close differentials of PHPT are other causes of hypercalcemia, which are enlisted in Box 1. Malignancy and granulomatous diseases are associated with suppressed levels of PTH. Some malignancies such as hepatocellular carcinoma, rarely produce ectopic PTH as a form of paraneoplastic syndrome. Another close differential is familial hypocalciuric hypercalcemia (FHH), which has a similar biochemical profile. Calculation of the fractional excretion of calcium (FeCa) in a 24-hour urine sample collected after discontinuing any diuretics is used to differentiate the two. Values less than 1% indicate FHH; however, the values can overlap in PHPT in cases of renal dysfunction and Vitamin D deficiency. In such cases, diagnosis should not be made till Vitamin D levels are replenished. And if the confusion is persistent, a mutational analysis should be done. This is important because for FHH, surgery is not curative. The genes to be tested are *CaSR*, *GNA11, AP2S1* for *FHH1, FHH2,* and *FHH3*, respectively.[73] Table 3 differentiates the biochemical profiles seen in various forms of hyperparathyroidism and its differentials.

Box 1: Causes of hypercalcemia

Parathyroid-dependent hypercalcemia

- Primary hyperparathyroidism
- Tertiary hyperparathyroidism
- Familial hypocalciuric hypercalcemia
- Lithium-associated hypercalcemia
- Antagonistic autoantibodies to the calcium-sensing receptor

Parathyroid-independent hypercalcemia

- Neoplasms
  - PTHrP-dependent
  - Other humoral syndromes
  - Local osteolytic disease (including metastases)
- PTHrP excess (non-neoplastic)
- Excess vitamin D action
  - Ingestion of excess vitamin D or vitamin D analogues
  - Topical vitamin D analogues
  - Granulomatous disease
  - William's syndrome
- Thyrotoxicosis
- Adrenal insufficiency
- Renal failure
  - Acute renal failure
  - Chronic renal failure with aplastic bone disease
- Immobilization
- Jansen disease
- Drugs
  - Vitamin A intoxication
  - Milk-alkali syndrome
  - Thiazide diuretics
  - Theophylline

Diagnosis and Evaluation

The two components of evaluation are biochemical confirmation and imaging. The biochemical evaluation involves Serum total and ionized calcium, intact PTH, creatinine, eGFR, 25-hydroxyvitamin D, albumin, serum phosphate and alkaline phosphatase. The significance of these has been discussed in the previous sections. Twenty-four-hour urine calcium and creatinine are needed to rule out a risk for renal stones and familial hypocalciuric hypocalcemia. While measuring PTH, the assay used should be either an intact second or a third-generation assay. There is no cross-reaction in the intact assays with PTH-related peptides and thus can differentiate hypercalcemia of malignancy from PHPT. The third-generation assays detect the whole PTH (1–84) and another molecule of whole PTH with a post-translation modification.[74] Box 2 outlies the list of investigations needed for a complete workup of a case of PHPT.

Imaging has no role in the diagnosis of PHPT. It is a biochemical diagnosis. Negative imaging does not preclude a surgical cure.[75] Imaging helps in anatomical localizing and screening of associated features. The screening imaging comprises DXA scan for BMD measurement, abdominal ultrasonography to rule out renal stones, and vertebral spine assessment to rule out silent vertebral fractures. The imaging for preoperative localization includes sonography of the neck, 4D computed tomography, magnetic resonance imagining, and functional imaging including sestamibi-SPECT and Fluorocholine PET. The advantages and disadvantages of each are discussed in Table 4.

Table 3: Biochemical profile of close differentials of PHPT

Forms of hyperparathyroidism	*Serum calcium level*	*PTH level*	*Phosphate level*	*Urinary calcium level*
Primary hyperparathyroidism	Increased	Raised/appropriately normal	Low	Fractional excretion >1%
Secondary hyperparathyroidism	Normal/low	Raised	Low: Vitamin D deficiency High: Renal failure	Dependent on cause
Tertiary hyperparathyroidism	Increased	Raised	Variable	Low before transplant
Normocalcemic primary hyperparathyroidism	Normal	Raised	Normal	<350 mg/24 hours
Familial hypocalciuric hypercalcemia	Increased	Raised/inappropriately normal	Normal	Fractional excretion <1%

Box 2: List of investigations for work up of PHPT

Blood investigations

- Serum total calcium
- Intact PTH
- Creatinine,
- eGFR
- 25-hydroxyvitamin D
- Ionized calcium
- Albumin
  - If low, calculate corrected calcium (mg/dL) = (0.8 [4.0-patient's albumin (gm/dL)] + total calcium (mg/dL)
- Serum phosphate
- Alkaline phosphatase

Urine tests

- 24-hour urine calcium and creatinine-screens for FHH
- If urine calcium <100 mg/24 hours, calculate CCCR
- CCCR = (24-hour calcium urine/calcium serum)/(24-hour creatinine urine/creatinine serum)

Imaging

- DXA-Measurements of bone mineral density at the lumbar spine, hip femoral neck, and distal radius
- Abdominal imaging for kidney stones or nephrocalcinosis
- Vertebral spine assessment
- Imaging for localization

Genetic testing

- Patients with PHPT less than 40 years with multigland disease and patients with a family history of PHPT or syndromes associated with PHPT

Management

Surgical Management

Parathyroidectomy is the treatment modality of choice in all symptomatic PHPT. Indications of surgery in asymptomatic individuals vary according to different guidelines and are summarized in Table 5. Traditionally bilateral neck exploration was done with cure rates of >95% and low complications. With the advent of precise localization techniques, and the availability of intraoperative PTH monitoring focused parathyroidectomy or minimally invasive parathyroidectomy can be attempted. It has similar cure rates with the reduced extent of surgery, length of incision, decreased recovery time, and postoperative pain.[75] After surgical excision, the biochemical normalcy follows with reduced urinary calcium.[76] Bone mineral density increases, and risk of fracture and renal stone decreases over time.[75,76] Cure is defined as normalization of either calcium and PTH levels in hypercalcemic PHPT, some cases remain hyper-parathyroid even after normalization of serum calcium, this is because of concomitant vitamin D deficiency or inadequate calcium intake, which may lead to the hungry bone syndrome. However, in cases of NPHPT cure cannot be defined until the PTH levels normalize. Persistent PHPT is defined as elevated levels of both calcium and PTH even after surgery.[75] Recurrent PHPT is defined as normalization of calcium and PTH levels for at least 6 months and more after surgery, but the develop biochemical evidence of PHPT again. The data on recurrent PHPT are scarce, so the exact incidence is not known.[75]

Non-surgical Management

Observation and medical therapy with close clinical follow-up is the cornerstone of non-operative management. This usually opts for those who do not meet the criteria for surgical management according to the various guidelines.[34,75] In addition, non-operative management is also recommended for those refusing surgery or those who are poor surgical candidates due to co-morbidities and poor health status. Ideal medical therapy should normalize the level of serum and urine calcium, PTH levels, increase BMD, and decrease the risk of fractures and nephrolithiasis. Currently, no drug available is close to the ideal requirement. Table 6 delineates the available drugs and their effect on various target organs.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism occurs due to an extrinsic abnormality in the calcium homeostasis as despite adequate PTH being secreted in response to the low serum ionized calcium, its levels are not raised. This leads to a state to a state of persistent hypocalcemia with raised serum PTH. The majority of symptoms and signs can be explained by acute and chronic hypocalcemia and elevated levels of PTH.

There are plenty of systemic causes which lead to secondary hyperparathyroidism and are enlisted in Box 3. However, for all practical purposes, CKD is the most common cause of secondary hyperparathyroidism and likewise, it is the most common complication of CKD, beginning even at the incipient stages of renal dysfunction. All the further discussion will be about secondary hyperparathyroidism caused by CKD.

Pathophysiology

Owing to the ground-breaking research in the past two decades there are multiple mechanisms elucidated in the pathogenesis of secondary hyperparathyroidism in the setting of CKD. They will be discussed briefly here. The basic tenet in pathogenesis is the increased production of PTH by the normal parathyroid glands due to extrinsic abnormalities. As the renal function deteriorates there is the retention of phosphate which in turn leads to decreased serum calcium and stimulation of PTH.[77] Phosphate also inhibits 1-alpha hydroxylation of vitamin D leading to further stimulus for PTH release.[78] Increased phosphate concentrations release FGF23 which indirectly increases serum PTH.[79] Phosphate levels also decrease the expression of CaSR on chief cells leading to unchecked PTH release. With progressive renal dysfunction, there is a decreased bioavailability of vitamin D due to multiple reasons and this leads to increased PTH secretion in calcium dependent as well as independent fashion.[80] In advanced renal disease, there is a decreased expression of CaSR on the chief cell membrane and PTH resistance on the target organs especially the skeletal system, both of which raise the serum PTH directly.[81,82] Some experimental mice models have shown increased cyclooxygenase 2 expression in the chief cells leading to parathyroid hyperplasia, this is important for both secondary and tertiary hyperparathyroidism.[83]

Clinical Manifestation

Skeletal System Involvement

Skeletal system involvement is invariable and characteristic in secondary hyperparathyroidism and is popularly called renal osteodystrophy. The most common manifestation is 2–4 times increased incidence of fractures when compared to the control population and associated increased mortality.[84] The range of symptoms comprise bone pain, stunted growth in children, and brown tumors, which are the most dreaded complication. They occur because of osteoclast and fibroblast proliferative activity. The fragility of the bones can be explained by bone resorption

Table 4: Imaging modalities used for preoperative localization of parathyroid glands with their advantages and disadvantages

Imaging modality	*Findings*	*Advantages*	*Disadvantages*
Ultrasonography (USG)	Hypoechoic nodule with well-defined hypervascular echogenic capsule	• Noninvasive • Inexpensive	• Unable to see ectopic mediastinal, retroesophageal, or retropharyngeal glands • Decreased sensitivity in multigland disease and small glands • Thyroid nodules and lymph nodes can cause false-positives Operator Dependent
Sestamibi-SPECT	Increased focal uptake and prolonged retention of the technetium-99m sestamibi	• Detects ectopic and posterior glands. • Lower radiation than 4D-CT • Operator-independent	• Long duration of time for the exam; • More expensive • Radiation exposure • Decreased sensitivity for multigland disease and small glands. • False-positives (lymph nodes, thyroid tissue, granulomatous disease).
Four-dimensional Computed Tomography (4D-CT)	Soft tissue nodule with peaked enhancement in arterial phase and washout in venous phase with polar vessel	• Rapid acquisition time • Superior anatomic information • Superior sensitivity • More successful in localizing small adenomas and multigland disease	• High radiation dose, • Intravenous contrast use • Some contrast artifact in neck veins can occur
Magnetic resonance imaging (MRI)	Homogeneous or marbled appearance with high intensity on T2-weighed images, intermediate to low intensity on T1-weighed images	• No radiation • Contrast not necessary • Superior anatomic information • Dixon fat suppression method	• Expensive • Long duration of study acquisition • Cannot use in patients with metal implants • Low specificity
18F-fluorocholine PET/CT	Focal tracer uptake	• Decreased radiation and acquisition time • Higher sensitivity • Ability to differentiate between parathyroid adenoma and hyperplasia based on maximal standardized uptake values	• Limited data on new tracer • Limited availability

Table 5: Variables to monitor in follow-up of asymptomatic PHPT and indications of surgery

Variables to monitor	*Criteria for surgery at initial evaluation*	*Schedule for follow-up evaluation*	*Criteria for surgery at follow-up*
Age	<50 years	NA	<50 years
Serum level of calcium	≥1 mg/dL above upper limit	Annually	≥1 mg/dL above upper limit
eGFR	<60 mL/minute	Annually	Reduction in eGFR <60 mL/minute
24 hours urinary calcium level	>400 mg/day	Repeat if kidney stone suspected	>400 mg/day
Biochemical stone profile	Increased risk	Repeat if kidney stone suspected	Increased risk
Renal imaging	Presence of nephrolithiasis or nephrocalcinosis	Repeat if kidney stone suspected	Development of kidney stone
DXA (spine, hip and forearm) Vertebral imaging	Tscore ≤−2.5 presence of a vertebral fracture	Every 1–2 years Repeat if vertebral fracture is suspected	TScore ≤−2.5 or reduction in BMD development of vertebral fracture

Table 6: Drugs available for medical management of PHPT with their effect on the biochemical profile

Drug	*Serum calcium level*	*Serum PTH level*	*Urinary calcium excretion*	*Bone mineral density*
Hydrochlorthiazide	No effect	No effect	Decreased	Inadequate data
Estrogen	No effect	No effect	No effect	Increased
Raloxifene	Decreased on long term treatment	No effect	No effect	Inadequate data
Alendronate	No effect	No effect	No effect	Increased
Cinacalcet	Decreased	Minimal decrease	No effect	No effect

Box 3: Differential diagnosis of secondary hyperparathyroidism

Gastrointestinal causes

- Inadequate dietary intake
- Food intolerance (milk/lactose)
- Dietary restriction
- Malabsorption
- Celiac disease
- Pancreatic disease
- Inflammatory bowel disease
- Cystic fibrosis
- Gastric bypass surgery

Vitamin D-related causes

- 25-hydroxylase deficiency
- Altered vitamin D metabolism
- Vitamin D dependent or resistant rickets or osteomalacia

Chronic kidney disease

- Hyperphosphatemia
- 1α-hydroxylase deficiency: Decreased 1,25-dihydroxyvitamin D
- Decreased clearance of parathyroid hormone: Accumulation of C-terminal parathyroid hormone
- Parathyroid hormone resistance

"Hungry bone" syndrome
Bisphosphonate treatment
Metastatic prostate cancer

by osteoclasts in the background of increased production of the bone matrix which remains unmineralized. Thus, altering the bone structure and making them weak.

Other System Involvement

It has been shown that elevated levels of PTH are associated with adverse cardiovascular events due to calcification of the vascular walls.[85] Other mechanisms contributing to such events are endothelial dysfunction, elevated sympathetic tone, and neuroendocrine activity. These can also be explained by dyslipidemia and increased insulin resistance in CKD which are independent of the degree of secondary hyperparathyroidism.

It has been shown that medical or surgical treatment of this condition leads to a better response to erythropoietin, which extrapolates that there is a cause-and-effect relationship between elevated PTH and anemia of CKD.[86] Many other systemic abnormalities such as immune dysfunction, dysfunction peripheral and central nervous system, glucose and lipid metabolism are seen but the causality is not established.

It is difficult to ascertain many clinical manifestations to elevated PTH or other factors secondary to hyperparathyroidism as they occur concomitantly with the progressive renal impairment which affects the bone as well as the health of other organs, independent of the effect of PTH.[87]

Diagnosis

The first is the biochemical assessment which relies on the elevated levels of PTH with a decreased or normal level of serum ionized calcium, which differentiates it from PHPT. The serum phosphate level is low as in PHPT. Serum albumin levels must be measured to be able to calculate the corrected value of serum calcium. Assessment of 25 hydroxy Vitamin D is done to assess the body stores. Alkaline phosphatase (ALP) levels are done as a marker of bone turnover.

Radiological investigations include the X-ray of skull, hands, pelvis, and spine. Bone mineral density is measured using DXA. And the radiological investigations to delineate the parathyroid gland function are performed as discussed previously.

Management

In contrast to PHPT, the mainstay is medical management with surgery reserved for select cases. Medical management focuses on the correction of abnormal pathogenic processes. Phosphate balance should be maintained with a diet low in phosphate and proteins and drugs that bind and cause the excretion of phosphate. Vitamin D supplementation should be done to deplete the body stores. The use of calcimimetics causes concentration dependent inhibition of PTH release. Examples are cinacalcet, velcacetide which allosterically modulate the CaSR.

Surgical management is reserved for those who are not responsive to the medical therapy. Patients with hypercalcemia and hyperphosphatemia have very high levels of PTH and severe renal osteodystrophy. However, many aspects of surgical therapy remain unanswered such as whether the parathyroidectomy should be performed before or after renal transplant and total excision of all four glands should be done with or without re-implantation.

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is characterized by elevated levels of ionized calcium in a setting of prolonged secondary hyperparathyroidism. By definition, PTH levels are elevated chronically. It occurs due to intrinsic abnormality of the parathyroid glands induced by long-standing external influences. The response of the glands is switched from reactive in secondary to semiautonomous in tertiary. A condition is similar to PHPT. However, the contrast from PHPT lies in the presence of a discernible disorder such as CKD or malabsorption in cases of tertiary hyperparathyroidism. The difference between secondary and tertiary is the normal levels of ionized calcium in the former and raised in the later.

Pathophysiology

The factors discussed in the pathogenesis of secondary hyperparathyroidism contribute in the development of semi-autonomous functioning of the parathyroid glands. With long-standing CKD, there is a decrease in vitamin D receptors (VDRs) on the surface of chief cells and a shift in set point of CaSR and an increase in FGF-23 production, which leads to unchecked PTH secretion despite high serum calcium.[88,89] This causes a progressive increase in the size and mass of parathyroid glands and culminates with nodular hyperplasia. The chief cells located in these nodular regions have further lower levels of VDRs and CaSR, setting up a vicious cycle of the autonomous state of secretion of PTH.

X-linked hypophosphatemic rickets, adult-onset (autosomal dominant) hypophosphatemic rickets, and oncogenic osteomalacia are rare genetic disorders associated with tertiary hyperparathyroidism. They are hereditary and treated with prolonged phosphate therapy which causes increased PTH secretion as explained above. Thus, over time can result in autonomous parathyroid gland functioning.[90,91]

Clinical Manifestation

Classically, tertiary hyperparathyroidism presents in individuals after renal transplant when the stimulus for PTH secretion has

normalized, but the PTH and ionized calcium levels remain high. The skeletal abnormalities are reversed after transplantation in most of the patients, some, however, have persistently elevated PTH with or without hypercalcemia. One study showed that in 52% of cases there isolated raised PTH, and 8% had raised PTH and calcium levels after 1 year of transplantation.[92] The symptomatology is similar to PHPT including bone pain, increased fracture, renal stones, pancreatitis, neuropsychiatric symptoms, and graft dysfunction.[93] The differential diagnosis to rule out are PHPT, prolonged use of vitamin D, or lithium therapy in CKD.

Management

Surgical removal of the parathyroid glands is the mainstay of treatment, which is indicated when the hypercalcemia and/or elevated PTH is persistent. There is no formal cut-off on the value of PTH to indicate operative management, but 2–9 times the upper limit of normal even with normal serum calcium is considered an indication.[94] In posttransplant individuals, severe hypercalcemic crisis warrants an urgent surgical intervention; otherwise, it is advised to wait for 12 months at least to allow calcium and phosphate levels to normalize. Subtotal or total parathyroidectomy with or without transplantation can be done based upon the individualized case-wise approach.[95] Very few studies have compared the two procedures and concluded that there was no difference in time of operation, days of stay in the hospital, laboratory parameters other than calcium and phosphate, but those undergoing total parathyroidectomy had more rates of hypocalcemia.[96] Another study concluded that total parathyroidectomy without autotransplantation appears to be protective against persistent and recurrent diseases.[97] The calcimimetic drugs can be tried in nonoperative management.

There is a need for longitudinal follow-up studies to delineate the natural history and response to management options in these subset of hyperparathyroidism cases.

Conclusion

Primary hyperparathyroidism has evolved into an incidentally detected asymptomatic disease with serum ionized calcium measurement. The mild manifestations are renal stones, hypercalcemia, fractures, and decreased no density. Biochemical diagnosis is followed by preoperative localization by imaging. Surgery is the frontline management with focal parathyroidectomy. But there is a lack of randomized trials to compare parathyroidectomy and observant management in those cases. There is also a dearth of data in the significance of neuropsychiatric and gastrointestinal symptoms in the present scenario and the effect of surgery on these manifestations. Secondary hyperparathyroidism occurs due to numerous disorders, CKD, and vitamin D deficiency being the most common culprits. The symptomatic involvement is skeletal predominantly, and diagnosis is made based on history and biochemical profile. Medical management of underlying disorders keeps it in check. However, surgery is sought when medical management fails. Some long-standing cases of secondary invariable progress to tertiary hyperparathyroidism and typically present postrenal transplant. The symptomatic profile and biochemical investigations are quite similar to primary but the history differentiates the two entities. Surgical intervention is modality of choice with total parathyroid glands excision.

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