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Parathyroid disease

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The role of parathyroid hormone in calcium and phosphate metabolism

Parathyroid hormone (PH) is secreted in a calcium mediated feedback loop from the parathyroid glands and its primary function is calcium and phosphate homeostases. Four parathyroid glands are anatomically situated posterior to the thyroid, within the central compartment of the neck. PH is secreted in response to a low serum calcium level and it affects three major organs, namely bone, kidneys and proximal small intestines. This negative feedback loop between the parathyroid gland and these target organs in relation to altered levels of serum calcium concentration is described as the parathyroid axis (Figure 1).[1,2]

The skeletal framework provides the largest reservoir for stored calcium (insoluble hydroxyapatite) and contributes to 99% of total body calcium.[3] It is here that PH accelerates bone resorption by influencing both osteoclasts and osteoblasts. PH secretion is a response to low levels of serum calcium by calcium-sensing receptors (CaSR) on parathyroid tissue. The secreted PH facilitates the differentiation of osteoblasts to osteoclasts by increasing the expression of RANKL, which is a receptor activator for the nuclear factor kappa B (NF-kB) ligand involved in the differentiation of osteoblasts to osteoclasts. Osteoprotegerin is a hormone that promotes preferential differentiation to osteoblasts, which is inhibited by PH. Osteoclastic activity functions to deconstruct bone (resorption) and release ionised calcium and phosphate.[1,4]

Direct calcium reabsorption in the kidneys is only partially influenced by PH, with its effects limited to the collecting ducts (CD) and distal convoluted tubules (DCT). However, the effect of PH on phosphate reabsorption in proximal convoluted tubules (PCT) is negative. The reduction in phosphate reabsorption facilitates the reduction of serum phosphate. This is an important indirect mechanism to increase serum calcium, as serum phosphate tends to form insoluble salts with serum calcium. The most important influence on calcium homeostasis that PH has on the kidneys is related to the production of activated citamin D (calcitriol), which is achieved by the stimulation of 1-alpha-hydroxylase from the PCT.[5] This enzyme catalyses calcitriol production from inactive vitamin D. Calcitriol further influences

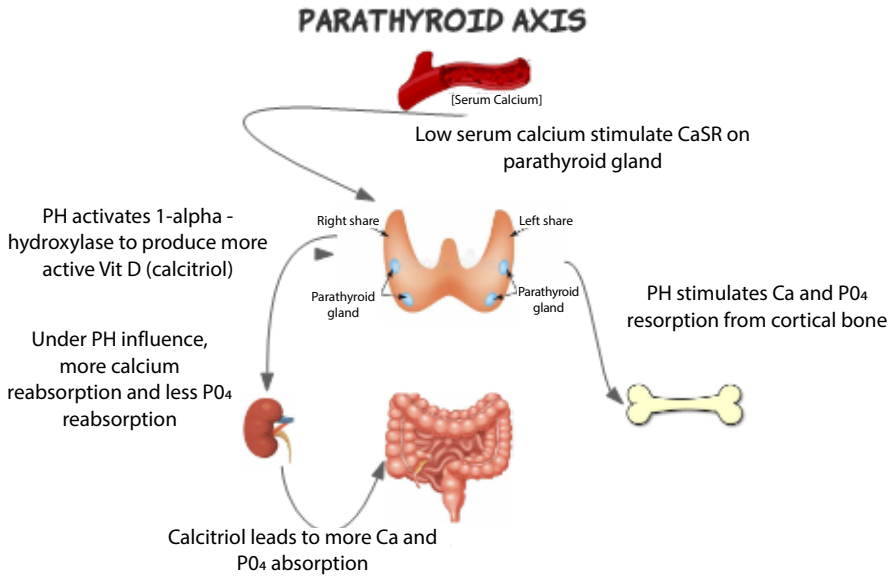

Figure 1: Illustration of parathyroid hormone (PH) release from parathyroid glands after calcium sensing receptors (CaSR) detect low serum calcium levels

calcium reabsorption in the DCT as well as calcium absorption in the proximal small bowel (duodenum).[1,6]

PH secretion seizes when serum calcium levels are elevated. The half-life of activated PH is only a few minutes as it quickly undergoes both renal and hepatic clearance. Calcitonin from the C cells of the thyroid gland is released in response to elevated serum calcium and functions to inhibit osteoclastic activity and promote renal excretion of calcium. Calcitonin plays a less influential role in calcium homeostasis compared to PH and calcitriol.[1,3]

From this basic physiological summary of calcium and phosphate metabolism, we can appreciate how parathyroid disease intimately influences serum and calcium levels. The natural history of parathyroid disease, albeit over- or underactivity, will thus invariably be related to underlying changes in serum calcium. The evaluation of abnormalities in serum calcium levels should therefore also be accompanied by PH, calcitriol, phosphate and albumin levels.[5]

Hyperparathyroidism

Hyperparathyroidism is described in three various forms: primary, secondary and tertiary. These each present with different biochemical pictures of calcium, phosphate and PH serum concentrations.

Primary hyperparathyroidism

Primary hyperparathyroidism (pHPT) is caused by an intrinsic dysfunction in the parathyroid gland, resulting in an unmitigated over secretion of the PH.[3] The most common cause is seen with parathyroid adenoma and less commonly parathyroid carcinoma. In some cases, it is seen in genetic disorders involving mutations of the CaSR such as familial hypocalciuric hypercalcaemia (FHH). Parathyroid hyperplasia is also seen in multiple endocrine neoplasia (MEN) syndrome type 1 and 2.[1,2,7] Long-term lithium and thiazide therapy can also cause a clinical picture that is indistinguishable from hyperparathyroidism.

The natural history of disease is dependent on its severity and often related to hypercalcaemia and increasing PH activity. In resource-rich environments that can afford regular screening, patients rarely present with overt symptoms. Patients often remain asymptomatic with relatively stable biochemical profiles for years, usually presenting after the fourth decade of life with a peak incidence within the seventh decade. In resource-limited environments, however, patients tend to present with symptoms of hypercalcaemia. These symptoms are as follows:

1. Neurological: neurocognitive impairment, depression and fatigue.
2. Gastrointestinal: nausea, vomiting, constipation, abdominal pain and pancreatitis. Peptic ulcer disease may present as part of MEN type 1 if there is an associated gastrinoma.
3. Renal: nephrolithiasis and nephrocalcinosis, renal dysfunction only in advanced stages.
4. Musculoskeletal: neuromuscular weakness, osteopenia, pathological fractures (particularly femur fractures) and bone pain.
5. Haematological: patients tend to be hypophosphatemic and display signs of haemolysis leading to anaemia. Platelet and leukocyte dysfunction is also not uncommon.
6. Cardiovascular: hypertension related to endothelial dysfunction and changes in left ventricular mass and function are directly attributable to elevated PH, while hypotension may occur as a result of polyurea. The cardiovascular effects of hypercalcaemia include prolongation of PR and QT intervals.[2,3,8]

Evaluation of patients who present these symptoms should include measurement of serum PH, calcium, phosphate, magnesium, albumin, vitamin D, calcitriol and 24-hour urine calcium excretion. Bone density scans (of the distal radius – this is a cortical rich site) and renal ultrasonography to detect renal stones are routinely performed in resource-rich centres.[2] Electrocardiography should be considered a standard.

Imaging has no utility in either diagnosing or excluding pHPT, and results are not used to select patients for surgical intervention. Preoperative fine needle aspiration may be considered in difficult cases of pHPT but should not be performed in suspected parathyroid carcinomas. Technetium Tc99m sestamibi is the dominant isotope in parathyroid scintigraphy, and in combination with ultrasonography there is increased sensitivity to and accuracy of adenoma localisation.[9] Dynamic computed tomographic (CT) imaging and magnetic resonance imaging (MRI) has a higher sensitivity to the sestamibi with a comparable positive predictive value, and is useful in identifying multiple or ectopic adenomas.[2]

It is important to note that anaesthetising a patient with unrecognised associated pheochromocytoma could result in fatality.[8] A high index of suspicion and knowledge of the association of the two conditions is crucial. Surgery remains the only definitive treatment, but is recommended for patients younger than 50 or those who display significant hypercalcaemia (> 1 mg/dL), osteoporosis, pathological fractures, bone pain, renal calculi and renal dysfunction. Surgery is recommended in patients who are older than 50 that present either with bone density T-scores of -2.5 and less or fragility fractures.[2,9]

Medical management is initiated prior to surgery, in patients who either refuse surgery or in whom surgery poses a substantial risk. The goal of medical management is to alleviate bone disease, hypercalcaemia and hypercalciuria. This is achieved in the following manner:

1. Vitamin D and calcium supplementation if necessary. A deficiency in vitamin D accelerates hyperparathyroidism. Daily restriction of calcium is not advised and an intake of 1 000–1 200 mg of calcium is actually recommend together with strict serum monitoring of both ionised and albumin corrected serum calcium levels.
2. Calcimimetic therapy. These are allosteric activators of CaSR that sensitise these to serum calcium and as a result mitigate PH secretion.

3. Thiazide diuretics. These are beneficial in reducing calcium excretion and help to prevent hypercalciuria and nephrolithiasis.[2,9]

There is no current evidence to support the use of antiresorptive therapies such as bisphosphonates in the setting of pHPT, and these do not correct the associated hypercalcemia.[2]

Preoperative optimisation is also aimed at the assessment of hydration status and the optimisation of intravascular volume in the hypercalcaemia-induced polyuria setting.[8]

Secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT) refers to the compensatory oversecretion of PH in response to abnormally low serum calcium, the most common cause being renal failure followed by vitamin D deficiency and gastrointestinal malabsorption.[1]

In chronic kidney disease (CKD), abnormalities in mineral metabolism such as hypocalcaemia, hyperphosphatemia and calcitriol deficiency lead to increased PH synthesis, secretion and ultimately parathyroid hyperplasia. This form of sHPT, also known as renal hyperparathyroidism (rHPT), is by far the most common form, which is attributable to the global prevalence of hypertension and diabetes and the implication thereof in the development of CKD. Renal hyperparathyroidism contributes to morbidity and mortality in CKD as it has direct effects on both vascular and bone-related outcomes.[6]

Early in the development of CKD, prior to the development of sHPT, pathological processes within the renal tubules lead to the altered homeostasis of the calcium, phosphate and vitamin D axis. Fibroblast growth factor 23 (FGF23) is a central hormone in these processes and begins to rise early in renal disease. It is a major phosphate regulatory hormone that is secreted by osteoblasts and osteocytes in response to high levels of phosphate, calcitriol and PH. Its receptor, FGF23 receptor 1 (FGFR1), is expressed in both renal distal tubule (DT) and parathyroid tissue, and it functions to reduce phosphate re-uptake in renal DT and down regulate 1-alpha-hydroxylase resulting in reduced levels of phosphate and calcitriol. It requires a co-receptor activation (alpha klotho), but this reduces with declining renal function, ultimately leading to low phosphate and increased PH. The clinical picture that ensues is one of hypocalcaemia, hyperphosphatemia, increased PH and reduced calcitriol. FGF23 has the primary function of lowering phosphate and calcitriol, but this ultimately leads to less calcitriol and thus hypocalcaemia leading to rHPT found in CKD.[6]

The clinical picture on presentation tends to overlap with features of CKD. Thirst and pruritus are the initial symptoms and, with disease progression, muscle weakness and fatigability ensue. Osteodystrophy and bone pain occur with continuing bone resorption. Excess phosphate is shifted to soft tissues (such as vasculature) leading to vascular calcifications, stiff vessels and myocardium. As mentioned before, hyperparathyroidism has effects on the myocardium independent of serum calcium.[5,6]

The first line of management is medical. It aims to compensate for reduced tubular function by supplementing vitamin D (ergocalciferol or cholecalciferol) which aids to reduce PH levels and correct hypocalcaemia. The use of active vitamin D analogues (bind to vitamin D receptors on parathyroid tissue and intestine) and vitamin D receptor activators have been described. These are effective in controlling PH. Vitamin D receptor activators may be categorised into non-selective and selective types, and both may be associated with hypercalcaemia and hyperphosphatemia. Control of phosphate can also be achieved by restricting its dietary intake by avoiding processed food and restricting protein. Phosphate binders are prescribed for patients on dialysis who cannot be fully protein restricted or where dietary restriction fails. In severe cases, where initial lines of therapy do not reduce rHPT, especially where renal osteodystrophy is particularly problematic, calcimimetics have been found beneficial in reducing bone resorption.[6,10]

Surgical management of rHPT includes renal transplantation or parathyroidectomy. A successful renal transplantation provides a normal renal architecture on which FGF23 and PH exert their effects. This results in effective phosphate excretion and calcium reabsorption, thus restoring mineral homeostasis leading to a reduction in PH secretion. Parathyroidectomy is recommended in patients who have severe end-stage renal disease, who are unlikely to receive renal transplantation, and in whom medical management has failed to correct hypercalcaemia or hyperphosphatemia with PH > 85 pmol/L.[6]

Tertiary hyperparathyroidism

With disease progression, the parathyroid glands may undergo significant hyperplasia and become unresponsive to hypercalcaemia in the setting of long-standing CKD with rPHT. It initially starts as a polyclonal and eventually leads to a monoclonal proliferation of parathyroid tissue with a loss of regulatory receptors. This may sometimes be referred to as an autonomous adenoma and is often resistant to medical treatment. The clinical picture that ensues is one of hypercalcaemia, very high PH levels and elevated phosphate.

Table I: Biochemical profiles of the various types of hyperparathyroidism

Type	PH	Serum calcium level	Serum phosphate level	Hypercalciuria	Alkaline phosphatase
Primary	Increased	Increased	Reduced	Increased	Increased
Secondary	Increased	Increased	Increased	Reduced	-
Tertiary	Increased	Increased	Reduced	Increased	-

Parathyroidectomy is reserved for cases that persist despite adequate medical management.[1,6]

Parathyroid surgery

Surgical considerations

Parathyroidectomy may be either total or subtotal, with or without a combined auto transplantation. Open procedure via a Kocher cervical incision, with bilateral exploration is the most well-described and recommended method. However, minimally invasive techniques together with intraoperative parathyroid hormone monitoring (IPM) in patients with pHPT with single adenomas have demonstrated to be 97–100% curative. The benefit of using supplemental IPM in these cases is that it provides real-time assessment of parathyroid function as it indicates residual hyperfunction. It may also be used in rHPT, but keeping in mind that PH is renally excreted, therefore, hormone level stabilisations are achieved only 15–20 minutes post excision.[2,9]

Anaesthetic considerations

Parathyroid surgery is usually done under general anaesthesia with the patient intubated and their neck slighted hyper-extended to facilitate good surgical exposure. Minimal blood loss is expected, but fluid status should be optimised prior to induction. Standard maintenance of anaesthesia with muscle relaxation together with the avoidance of hypoventilation/hyperventilation as acidosis increases calcium levels and vice versa. In the absence of postoperative complications such as haematoma, bleeding, recurrent laryngeal nerve injury and hypocalcaemia, emergence is usually uneventful. The recommendation is a postoperative admission into a high dependency unit for monitoring of hypocalcaemia, bleeding and haematoma formation with subsequent airway obstruction.[8,9]

Hypoparathyroidism

Hypoparathyroidism most commonly occurs as a complication of anterior neck surgery. Other rare non-surgical causes are either autoimmune or part of a larger syndromic disease (22q11.2 deletion syndrome). It should be suspected when a patient's biochemical profile displays a low ionised or albumin-corrected calcium level together with an inappropriately normal or low PH level.[11]

Patients will often present with a history of neck/thyroid surgery along with various systemic features such as the following:

1. Neurological: lethargy, neuronal irritability, depression, paraesthesia
2. Ocular: cataracts
3. Cardiac: hypotension, heart failure, prolonged QT syndrome
4. Neuromuscular: positive Chvostek sign (facial contraction after facial nerve stimulation) or positive Trousseau sign (finger/wrist contraction elicited after inflation of blood pressure cuff above systolic blood pressure on ipsilateral arm)[3]

Emergency management is targeted at correcting hypocalcaemia induced tetany and seizures through the administration of at least 93 mg of elemental calcium over a 10–15 minute period. Other long-term management methods include treatment of underlying aetiology, calcitriol and calcium supplementation, as well as avoiding furosemide and using thiazide diuretics instead.[3,11]

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