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REVIEW ARTICLE

Primary hyperparathyroidism: concepts for the general surgeon

Hiperparatiroidismo primario: conceptos para el cirujano general

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Abstract

During the last decades, the incidence of primary hyperparathyroidism has been increasing, most probably related to the greater accessibility to diagnostic studies; however, the most common form of clinical presentation of primary hyperparathyroidism is asymptomatic in more than 80% of patients. Diagnosis is less frequent due to associated renal (urolithiasis) or bone (osteitis fibrosa cystica) complications. A benign tumor of the parathyroid gland (single adenoma) is the main cause of this disease. Therefore, its treatment is usually surgical. Despite this, the management of this pathology by the general surgeon is not frequent. This article reviews key concepts for the diagnosis and management of this disease by the resident physician and specialist in General Surgery.

Keywords: parathyroid glands; primary hyperparathyroidism; parathyroid hormone; parathyroid neoplasms; adenoma; hypercalcemia; parathyroidectomy.

Resumen

Durante las últimas décadas, la incidencia del hiperparatiroidismo primario ha venido en aumento, muy probablemente relacionado con la mayor accesibilidad a los estudios diagnósticos; sin embargo, la forma más común de presentación clínica del hiperparatiroidismo primario es asintomática, en más del 80 % de los pacientes. En la actualidad, es menos frecuente el diagnóstico por las complicaciones renales (urolitiasis) u óseas (osteitis fibrosa quística) asociadas. Un tumor benigno de la glándula paratiroides (adenoma único), es la principal causa de esta enfermedad. Por tanto, su tratamiento usualmente es quirúrgico. A pesar de ello, no es frecuente el manejo de esta patología por el cirujano general. En este artículo se revisan conceptos claves para el diagnóstico y manejo de esta enfermedad para el medico residente y especialista en Cirugía General.

Palabras clave: glándulas paratiroides; hiperparatiroidismo primario; hormona paratiroidea; neoplasias de las paratiroides; adenoma; hipercalcemia; paratiroidectomía.

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Introduction

The first description of the parathyroid glands as an organ was made in 1850 in the London Zoo during a necropsy of a rhino. The first parathyroid surgery was performed in 1925 in Vienna by Félix Mandl in a patient with osteitis fibrosa cystica. During the same year, biochemist James B. Collip, in Canada, discovered the parathyroid hormone (PTH), after participating in the group of researchers who isolated insulin and adrenocorticotropic hormone (ACTH).

Primary hyperparathyroidism (PHPT) is the third endocrine disorder in frequency[1], which is characterized, in the absence of a recognized stimulus, that one or more parathyroid glands secrete PTH in excess, resulting in hypercalcemia. The prevalence is estimated to be 0.85% and its current incidence is approximately 50 cases per 100,000 person-year in the United States, being more frequent in women (2 to 3:1) between 50 and 65 years of age[2].

The clinical presentation has varied in the last 40 years, from symptomatic pictures associated with severe hypercalcemia, kidney stones and bone disease (osteitis fibrosa cystica), up to an asymptomatic condition, more common in the present, incidentally diagnosed with routine examinations (serum calcium, biochemistry tests, bone densitometry, etc.).

Embryology and anatomy

The parathyroid glands develop between the fifth and seventh weeks of gestation. Superior glands originate from the fourth branchial bag and are generally located towards the cricotracheal junction, between the thyroid tissue and the recurrent laryngeal angle nerve, while the lower glands originate from the third branchial pouch. About 44% found in the thyrothymic ligament, 26% in thymic horn, 17% at the lower pole of the thyroid gland, 2% in the mediastinum, and 11% are distributed in the upper carotid bed or inside the thyroid[3].

In 91% of people there are four glands, in 5% there are three, and in 4% there are five or more. Usually, each measure between 5 and 7 mm. Each parathyroid tissue can weigh between 90 and 130 mg. In 83% of cases they are oval, in 11% elongated, 5% kidney-shaped, and in 1% multilobed. They are generally accompanied by periglandular fat tissue, and in 80% of cases are located in a contralateral mirror fashion[3]. Usually the parathyroid glands receive their supply from the lower thyroid artery; however, up to 45% of patients, the upper glands may receive branches of the superior thyroid artery[4].

Calcium homeostasis

The average daily calcium intake is 500 to 1000 mg. Its absorption occurs mainly in the duodenum and proximal jejunum. In the kidney, almost all of the filtered calcium is reabsorbed at the proximal tubule and loop of Henle, through the sodium pump. In the distal tubule, absorption calcium is mediated by PTH. The daily calcium loss is approximately 100 mg by perspiration and 800 mg in the feces. The oldest body deposit of calcium are the bones, which contains approximately 1000 gr[5].

Control of calcium and phosphorus serum levels is complex, because it not only depends on the intake, but the participation of organs such as intestine (where absorption is mediated by metabolites of vitamin D), kidney (excretion), liver (fragmentation of PTH), bone (deposit and release), skin (activation of vitamin D_3 by ultraviolet irradiation of 7-dihydroxycholesterol), parathyroid glands (parathyroid hormone), and thyroid gland (where C cells or parafollicular cells produce calcitonin, which decreases bone resorption due to its antagonistic effect to PTH).

Serum calcium concentrations normally should be in a very narrow range between 8.5-10.5 mg/dl or 2.1-2.6 mmol/l, which is the value required for the optimal performance of multiple physiological processes, intra and extracellular in the body. To achieve the exact regulated concentration depends on the relationship between intestinal absorption, renal excretion and uptake and bone release, processes that are in turn regulated by the action of parathyroid hormone, the vitamin D_3 and, to a lesser extent, calcitonin.

PTH is the main regulatory hormone of calcium homeostasis. It is produced by the main cells of the parathyroid gland, in form of a 110 aminoacid prohormone, which splits and eventually becomes the proper hormone, a polypeptide of 84 aminoacids. It has a biological active portion corresponding to the N-terminal amino group (residues 1-34) and an inactive one that corresponds to C-terminal carboxyl group (residues 35 to 84). The half-life of intact PTH is approximately 6 minutes in the N-terminal fragment and almost 1 hour in the C-terminal fragment. Its degradation occurs mainly in the liver.

Calcium is the main body mineral, but only its ionized form is physiologically active. In serum, 47% occurs in ionized form, 45% protein bound, and 8% in the form of organic anions. Its function is to stimulate muscle contraction, to produce excitability of the nervous system, the formation of bone matrix and facilitate signal transduction[5].

Hypocalcemia is the main physiological stimulus of the main cells of the parathyroid glands, where the synthesis and secretion of the parathyroid hormone is regulated through three receptors:

1. The vitamin D receptor (VDR) which, by binding to it, decreases the synthesis of PTH.

2. The specific calcium receptor (CaER) that, being occupied by this element, it inhibits the synthesis and secretion of PTH.

3. The Fibroblast Growth Factor receptor (FGF-R) and the transmembrane protein "Klotho" form a complex that is stimulated by Fibroblast Growth Factor 23 (FGF-23). FGF-23 is a hormone that is produced in osteocytes and osteoblasts when phosphate and calcitriol levels increase. FGF-23 inhibits the secretion of PTH in the parathyroid glands and decreases reabsorption of phosphate in the kidney proximal tubule.

PTH acts on bone osteocytes, osteoclasts and osteoblasts, increasing the calcium level. In the kidney, it promotes calcium retention and phosphate excretion and stimulates the absorption of calcium in the intestine.

At the level of the renal proximal tubule, usually there is a reciprocal exchange between calcium and phosphorus to maintain their levels stable. Likewise, 1α-hydroxylase allows the activation of vitamin D (calcitriol). The action of 1α-hydroxylase is suppressed by FGF-23. Hypocalcemia and hyperphosphatemia stimulate production of PTH, while vitamin D inhibits it [6-8] (Table 1).

Pathophysiology and causes of primary hyperparathyroidism

In PHPT, the metabolic disorder is located in the parathyroid glands due to loss control of the synthesis and secretion of PTH. In more than 80% of the cases, hypercalcemia is detected asymptomatic, associated with elevated PTH. However, hypercalcemia can also occur with normal or minimally elevated PTH values. Normocalcemic PHTP[8] is one of the forms of presentation of the PHTP, and there are, in repeated tests, elevated levels of PTH with normal serum calcium. For its diagnosis, other causes of secondary hyperparathyroidism must be excluded, such as kidney disease, vitamin D deficiency, drugs or malabsorption syndromes, among others.

Familial hypocalciuric hypercalcemia (FHH), a hereditary benign condition, is one of the main differential diagnoses of the PHTP. It occurs in young individuals with chronic hypercalcemia and normal or slightly elevated PTH levels[9]. According to clinical guidelines, the calcium/creatinine clearance ratio (CCCR) is the biochemical index of choice to differentiate between PHTP and FHH. A quotient less than 0.01 it is suggestive of FHH and one greater than 0.02 of PHTP. Patients with FHH do not require surgical treatment [10].

In approximately 86% of cases of PHTP, the cause is a single parathyroid adenoma, in 9% diffuse or nodular hyperplasia of one or several glands, in 3% double adenoma and in 1-2% carcinoma.

When there is a carcinoma, usually there are a compromised target organs, such as osteoporosis, pathological fracture, urolithiasis, pancreatitis, or

Table 1. Main mechanisms of control of calcium, phosphorus, and vitamin D.

	Parathyroid gland	Kidney	Bone	Intestine
Stimulus	Hypocalcemia and hyperphosphatemia	Hypocalcemia, hyperphosphatemia and elevation of PTH	Hyperphosphatemia and elevation of 1,25 Vit D3	Hypocalcemia
Response	Elevation PTH	Increases synthesis of 1.25 Vit D3	Release FGF-23	
Action	FGF-23: decreases PTH	FGF-23: Decreases 1.25 Vit D3, increases reabsorption of calcium and phosphorus excretion	PTH: Releases calcium and phosphorus and increases synthesis of FGF-23	1.25 Vit D3: Increases calcium and phosphorus absorption
	1.25 Vit D3: decreases PTH	PTH: Increases 1.25 Vit D3, increases calcium reabsorption and excretion		

* PTH: parathyroid hormone; 1.25 Vit D3: calcitriol; FGF-23: fibroblast growth factor-23.

disorder of consciousness. In 75% of cases, the serum calcium level is above 14 mg/dl and intact PTH elevated more than 4 times its normal value. It can course with vocal fold paralysis, in 50% of cases a nodule is palpable in the neck and in 75% its size is greater than 2 cm[11,12].

Other causes of primary hyperparathyroidism

Hereditary syndromes

In 95% of cases, PHTP presentation is sporadic[13]; however, in rare cases, it presents at early ages as part of familial syndromes. Familial hyperparathyroidism includes a group of disorders where PHTP is inherited, usually, like an autosomal dominant feature.

Multiple endocrine neoplasia syndrome (MEN) type 1, is caused by mutations inactivating genes in the NEM1 gene (11q13) that encodes the protein menin, a tumor suppressor. Initially described in 1954, it is the most common cause of familial PHTP, representing approximately 2-4% of all cases[13]. It is characterized by a predisposition to develop endocrine tumors at the level of the pituitary, parathyroid and neuroendocrine pancreatic and gastrointestinal tract tumors. The association of the NEM1 gene mutation with the sporadic or familial presentation of parathyroid adenomas has been well documented, while its association with parathyroid carcinoma is rare. PHTP is the more frequent endocrine disorder, it presents in around 90% of patients between 20 and 25 years old and usually there is a multiglandular involvement with growth of all glands.

The more recently described MEN type 4 it is similar to NEM1. Those affected develop parathyroid, pituitary, pancreatic, adrenals and, rarely, cervix and testes tumors. It is caused by inactivating mutations in the CDKN1B gene, which encodes the p27 protein, which acts as a regulator in the progression of the cell cycle. More than 80% of those affected due to this syndrome have primary hyperparathyroidism[14].

MEN type 2A syndrome, caused by mutations in the RET proto-oncogene on the chromosome 10, is characterized by finding of medullary thyroid carcinoma, pheochromocytoma, and hyperplasia or parathyroid adenoma. PHTP occurs in 20-30% of cases, usually with mild presentation or asymptomatic symptoms. Progression to malignant parathyroid adenomas is rare[13].

Hyperparathyroidism mandibular tumor syndrome (HPT-TM) is caused by mutations in the HPRT2 gene on chromosome 1, causing parathyroid tumors, ossifying fibromas of the mandible, kidney lesions (Wilms tumor, renal papillary carcinoma, cystic disease) and PHTP[14]. In more than 95% of patients, the first manifestation is primary hyperparathyroidism, with a more aggressive behavior due to severe hypercalcemia and often unusually high frequency of parathyroid carcinoma (10-15%)[13].

Another hereditary syndrome is the Familial Isolated Hyperparathyroidism. It is uncommon, and is characterized by the presence of primary hyperparathyroidism caused by single or multiple parathyroids tumors in at least 2 first degree relatives and in the absence of other tumors or endocrine disorders. The specific mechanism is unknown, but they have been detected mutations in the NEM1 gene (20-23%), in the gene CaER (specific calcium receptor, in 14-18%) and in the HRTPT2 gene, in a lower percentage (Table 2).

Radiation exposure

Patients with PHTP may have a history of radiation of head and neck, in a range of 20 to 40 years prior to the development of the condition. The most representative example is a cohort of 61 workers at the nuclear plant in Chernobyl in 1986 where 15 of them developed PHTP. The mean exposure was between 0.3 to 8.7 Gy. It has not been demonstrated differences in clinical course or recurrence between exposed and unexposed patients. However, in exposed patients it was associated with thyroid tumors[15].

Drugs

Lithium therapy and thiazide diuretics have been associated as risk factors for PHTP[16]. More recent experience with thiazides has suggested that hypercalcemia, in this context, possibly masks the underlying state of the PHTP, and is not likely to be reversed when the diuretic is suspended[17].

Diagnosis

Most cases of PHTP are diagnosed incidentally by routine laboratories or within the osteopenia or urolithiasis follow-up. Clinically, it presents as asymptomatic hypercalcemia in about 80% of cases. Symptomatic PHTP may manifest with bone pain, fatigue, weight loss, peptic ulcer, pancreatitis, nephrolithiasis, accelerated arteriosclerosis, cognitive deficit, and anxiety.

Table 2. Characteristics of hereditary syndromes in primary hyperparathyroidism.

Characteristics	NEM 1	NEM 2A	NEM 4	HPT-TM	HPT familiar
Hyperparathyroidism	✓	✓	✓	✓	✓
Pancreatic tumors	✓		✓		
Pituitary adenomas	✓		✓		
Medullary thyroid cancer		✓			
Pheochromocytoma		✓		✓	
Mandible and kidney tumors					
Heritage	AD	AD	AD	AD	AD
Gene mutation	NEM 1	RET proto oncogene	CDKN1B	HRPT2	NEM1-RECa-HRPT2

* MEN: multiple endocrine neoplasia; HPT: hyperparathyroidism; HPT-TM: hyperparathyroidism-mandibular tumor; AD: autosomal dominant; CDKN1B: cyclin-dependent kinase inhibitor 1B; CaER: specific calcium receptor.

Labs frequently show elevated PTH and serum calcium, and increased of urinary calcium excretion, and the typical pattern of salt and pepper granules on radiographs bone, compatible with osteitis fibrosa cystica, osteopenia of the third distal part of the clavicle, subperiosteal resorption of the distal phalanges, bone cysts or brown tumors.

Scintigraphy performed with Tc99m (technetium)-Sestamibi, in planar images such as single photon emission computed tomography (SPECT), is useful in the localization of parathyroid adenomas, especially in those of size greater than 500 mg[18,19]. Sensitivity and specificity improves when SPECT images are fused with images from computed tomography (Figure 1), preferably from hybrid equipment, passing the sensitivity of 83% to 96% and specificity from 80 to 93%, more evident advantages in smaller adenomas of about 210 mg[20]. Sensitivity is 58% in the case of hyperplastic glands[21]. When conventional nuclear medicine imaging (SPECT) is negative, an alternative is to perform a positron emission tomography (PET-CT) with C11-Methionine, with F18-Choline or C11-Choline[22,23].

It is recommended to have a thyroid ultrasound to rule out a concomitant thyroid disease. Other images such as contrast CT, MRI, angiography with selective PTH or PET scan, are only used in case of negative scintigraphy, recurrence, or difficult location of the gland or ectopic parathyroid tissue[24].

As previously explained, a differential diagnosis is with benign familial hypocalciuric hypercalcemia, with normal or slightly elevated PTH. It is generally diagnosed by persistent hypercalcemia after partial parathyroidectomy[25].

Although primary carcinoma of the parathyroid is suspected, biopsy with fine needle is not recommended due to its low specificity and the possibility of developing parathyromatosis.

Surgery is the recommended treatment in the PHTP (Table 3) for the symptomatic or asymptomatic patient, having target organ involvement (osteopenia, urolithiasis, decreased blood glomerular filtration rate, peptic ulcer, pancreatitis, or neuromuscular disorder).

The experienced surgeon is able to identify the affected gland(s) in 95% of the cases. Image fusion (SPECT-CT) and the measurement of iPTH (intact molecule) in the course of surgery, have allowed to make more therapeutic decisions successful, reducing the recurrence rate of PHTP to less than 5%[26]. Radioguided surgery and the decision to perform a minimal invasive approach will depend on available technology and on the experience of the surgeon (Figures 2 and 3).

Usually it is an outpatient procedure, the patient is discharged with calcium supplements (3 g/day) and calcitriol (0.25 mcg/day). The control is done in 3 weeks with new iPTH values, serum alkaline phosphatase, calcium, and phosphorus.

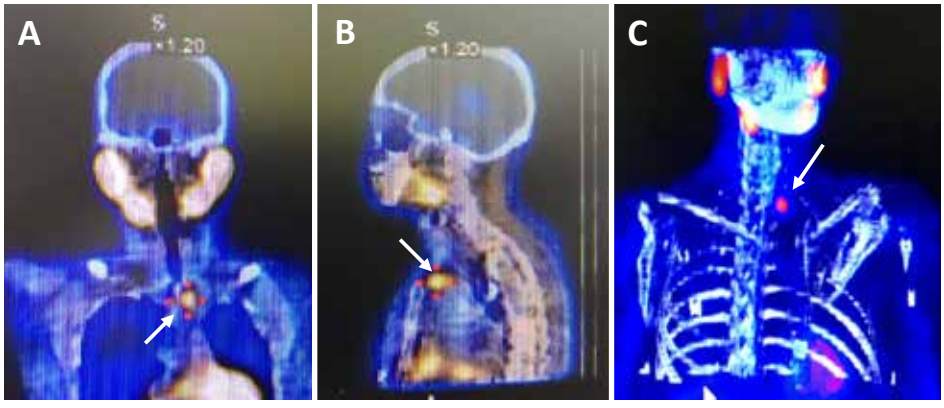

Figure 1. Parathyroid scan with SPECT-CT showing hyperuptake of the left lower parathyroid gland (white arrows)

In patients with high surgical risk, or who reject the procedure, a strict annual follow-up with calcium, creatinine and bone densitometry levels should be recommended. In some cases, with symptomatic hypercalcemia is recommended to maintain a good hydration, restriction of calcium intake, ensure normal levels of vitamin D, and even the use of calcium mimetics. It is recommended that the therapeutic decision be taken between the surgeon, the endocrinologist, and the patient[27-29].

Radical surgery is recommended for primary carcinoma (after correction of the severe hypercalcemia), with ipsilateral hemithyroidectomy, contralateral exploration and thymectomy, with lymphadenectomy in case of documented histological involvement.

Complications of surgical management

The most common complication is transitory hypocalcemia, which occurs between 15% and 30% of patients, and represents 7% of postoperative readmissions for intravenous calcium administration. When the patient is admitted in Emergencies and symptomatic hypocalcemia is documented, oral and intravenous calcium should be administered simultaneously. It is recommended calcium gluconate infusion two vials in 100 cc of normal saline or dextrose in water, to pass in 15 minutes (do not use ringer's lactate by gluconate precipitation), and continue with one vial every 6 hours until symptoms are controlled. Oral calcium is administered (1.5-3 gr) every 6 hours, in carbonate or citrate presentation, and calcitriol (0.25 mcg) every 8 hours. With this management, the patient is discharged in 12 to 24 hours in the vast majority of cases.

In some cases, postoperative hypocalcemia is severe and prolonged, despite having a normal or slightly elevated PTH, and can be associated with hypophosphatemia, hypomagnesemia, and hyperkalemia, requiring hospital management with cardiac monitoring, oral and intravenous supplementation of calcium, magnesium, and calcitriol. This condition is known as "hungry bone syndrome" and occurs in approximately 13% of patients undergoing parathyroidectomy

Table 3. Indications for surgical management of primary hyperparathyroidism.

- Patient under 50 years old
- Serum calcium greater than 12 mg/24 hours
- Calciuria greater than 400 mg/24 hours
- Decrease in creatinine clearance greater than 30% for age
- Lumbar, hip or distal radius densitometry with T-score less than -2.5
- Patients with impossibility of medical follow-up

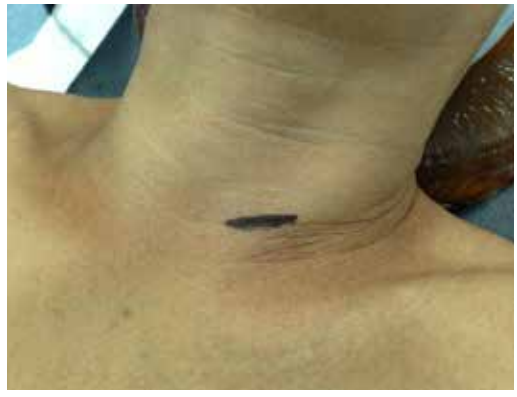

Figure 2. Left retrothyroid surgical approach.

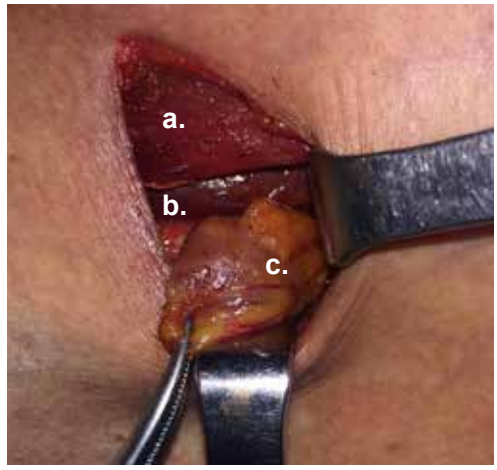

Figure 3. Left inferior parathyroid adenoma. a. Sternothyroid muscle; b. left thyroid lobe; c. parathyroid adenoma.

for PHTP. Generally, affects patients with osteitis fibrosa cystica and patients who have received therapy with calcium mimetics for a long time. They are also considered risk factors to develop it in those who are under 45 years old, with obesity, high levels of alkaline phosphatase and normal or low preoperative serum calcium levels[8,30,31]. Institutions with high volume of parathyroid surgery and with enough resources have used the cryopreservation of parathyroid tissue to re-implant it in case of severe hypoparathyroidism difficult to manage[32].

Bleeding, infection, or recurrent laryngeal nerve injury appear approximately in 1% of cases. The perioperative mortality is 0.3%[33-35].

The least desired complication by the surgeon is the impossibility of finding the affected gland or glands and the consequent persistence of hyperparathyroidism. Failures are generally present in the preoperative location, in the cervical examination or by underestimating the number of parathyroid glands with hyperplasia versus adenomas. Tominaga reported an incidence of persistent PHPT of 4%, and a 1.6% reoperation rate due to this cause[35].

Parathyromatosis is the seeding of multiple foci of benign and hyperfunctioning parathyroid tissue in the soft tissues of the neck or mediastinum, product of the rupture of the capsule of the parathyroid gland during the surgical exploration, fine needle biopsy, or percutaneous use of sclerotherapy with alcohol. These last two procedures are not recommended routinely[35].

Conclusions

Primary hyperparathyroidism is a common cause of hypercalcemia. Its clinical presentation has evolved to a condition mostly asymptomatic in the population, whose diagnosis is made from routine biochemical tests. In young patients, diagnostic approach must be careful; in these cases, it can be a component of multiple hereditary endocrinology abnormalities that, although they represent less than 5% of the PHTP, affect this age group more frequently. Surgery is the only curative treatment of this disease; it is recommended in young symptomatic patients, or in those asymptomatic who are at risk to present target organ involvement. Currently, the pre-surgical study with images diagnostic tests (scintigraphy or SPECT) allow to locate the adenoma more precisely, avoiding recurrences and allowing minimal invasive approach.

Compliance with ethical standards

Informed consent: This study is a review of the literature, and as such there is no need to informed consent or approval of the Institutional Ethics Committee.

Conflict of interest: The authors declare no conflicts of interest.

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Author's contribution: Conception and design of the study, acquisition, analysis and interpretation of data, writing, critical review and final approval of the manuscript: Gabriel Sánchez-De Guzmán and Aníbal Ariza.

References

1. Madkhali T, Alhefdhi A, Chen H, Elfenbein D. Primary hyperparathyroidism. Turkish J Surg. 2016;32:58–66. https://doi.org/10.5152/UCD.2015.3032
2. Griebeler ML, Kearns AE, Ryu E, Hathcock MA, Melton LJ, Wermers RA. Secular trends in the incidence of primary hyperparathyroidism over five decades (1965-2010). Bone. 2015;73:1–7. https://doi.org/10.1016/j.bone.2014.12.003
3. Akerstrom G, Malmaeus J, Bergstrom R. Surgical anatomy of human parathyroid glands. Surgery. 1984;95:14–21.
4. Arrangoiz R, Cordera F, Caba D, Muñoz-Juárez M, Moreno E, Luque E. Parathyroid embryology, anatomy, and pathophysiology of primary hyperparathyroidism. Int J Otolaryngol Head & Neck Surg. 2017;06:39–58. https://doi.org/10.4236/ijohns.2017.64007
5. Bloom MB, Norton JA. Parathyroid. In: Norton J, Barie PS, Bollinger RR, Chang AE, Lowry S, Mulvihill SJ, *et al*, editors. Surgery Basic Science an Clinical Evidence. 2nd ed. Nueva York: Springer; 2008. p. 857-77.
6. Bellorin-Font E, Ambrosoni P, Carlini RG, Carvalho AB, Correa-Rotter R, Cueto-Manzano A, *et al*. Guías de práctica clínica para la prevención, diagnóstico, evaluación y tratamiento de los trastornos minerales y óseos en la enfermedad renal crónica (TMO-ERC) en adultos. Nefrologia. 2013;33(suppl1):1–28. https://doi.org/10.3265/Nefrologia.pre2013.Feb.11945

7. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: Pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol. 2011;6:913–21. https://doi.org/10.2215/CJN.06040710
8. Lau WL, Obi Y, Kalantar-Zadeh K. Parathyroidectomy in the management of secondary hyperparathyroidism. Clin J Am Soc Nephrol. 2018;13: 952–61. https://doi.org/10.2215/CJN.10390917
9. Blackburn M, Diamond T. Primary hyperparathyroidism and familial hyperparathyroid syndromes. Aust Fam Physician. 2007;36:1029-33.
10. Lee JY, Shoback DM. Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab. 2018;32:609–19. https://doi.org/10.1016/j.beem.2018.05.004
11. Myers E, Suen Y, Watson C. Cancer of the parathyroid. In: Myers E, Suen Y, eds. Cancer of the Head and Neck. 3th ed. Philadelphia: W.B Saunders; 1996. p. 516–24.
12. Rodríguez-Portillo M, Rodríguez-Ortiz ME. Secondary hyperparthyroidism: Pathogenesis, diagnosis, preventive and therapeutic strategies. Rev Endocr Metab Dis. 2017;18:79–95. https://doi.org/10.1007/s11154-017-9421-4
13. Giusti F, Cavalli L, Cavalli T, Brandi ML. Hereditary hyperparathyroidism syndromes. J Clin Densitom. 2013;16:69-74. http://doi.org/10.1016/j.jocd.2012.11.003
14. Falchetti A. Genetics of parathyroids disorders: Overview. Best Pract Res Clin Endocrinol Metab. 2018;32:781-90. https://doi.org/10.1016/j.beem.2018.09.011
15. Boehm BO, Rosinger S, Belyi D, Dietrich JW. The Parathyroid as a target for radiation damage. N Engl J Med. 2011;365:676-8. https://doi.org/10.1056/NEJMc1104982
16. Szalat A, Mazeh H, Freund HR. Lithium-associated hyperparathyroidism: Report of four cases and review of the literature. Eur J Endocrinol. 2009;160:317-23. https://doi.org/10.1530/EJE-08-0620
17. Griebeler ML, Kearns AE, Ryu E, Thapa P, Hathcock MA, Melton LJ, Wermers RA. Thiazide-associated hypercalcemia: Incidence and association with primary hyperparathyroidism over two decades. J Clin Endocrinol Metab. 2016;101:1166-73. https://doi.org/10.1210/jc.2015-3964
18. Greenspan BS, Dillehay G, Intenzo C, Lavely WC, O'Doherty M, Palestro CJ, *et al*. SNM practice guideline for parathyroid scintigraphy 4.0. J Nucl Med Technol. 2012;40:111-8. https://doi.org/10.2967/jnmt.112.105122
19. Hindié E, Ugur Ö, Fuster D, O'Doherty M, Grassetto G, Ureña P, *et al*. 2009 EANM parathyroid guidelines. Eur J Nucl Med Mol Imaging. 2009;36:1201-16. https://doi.org/10.1007/s00259-009-1131-z
20. Sandqvist P, Nilsson IL, Grybäck P, Sanchez-Crespo A, Sundin A. SPECT/CT's advantage for preoperative localization of small parathyroid adenomas in primary hyperparathyroidism. Clin Nucl Med. 2017;42:e109-14. https://doi.org/10.1097/RLU.0000000000001447
21. Caldarella C, Treglia G, Pontecorvi A, Giordano A. Diagnostic performance of planar scintigraphy using 99mTc-MIBI in patients with secondary hyperparathyroidism: A meta-analysis. Ann Nucl Med. 2012;26:794-803. https://doi.org/10.1007/s12149-012-0643-y
22. Yuan L, Liu J, Kan Y, Yang J, Wang X. The diagnostic value of 11C-methionine PET in hyperparathyroidism with negative 99mTc-MIBI SPECT: A meta-analysis. Acta Radiologica. 2017;58:558-64. https://doi.org/10.1177/0284185116661878
23. Orevi M, Freedman N, Mishani E, Bocher M, Jacobson O, Krausz Y. Localization of parathyroid adenoma by 11C-Choline PET/CT: preliminary results. Clin Nucl Med. 2014;39:1033-8. https://doi.org/10.1097/RLU.0000000000000607
24. Walker MD, Silverberg SJ. Primary hyperparathyroidism. Nat Rev Endocrinol. 2018;14:115-25. https://doi.org/10.1038/nrendo.2017.104
25. Fraser WD. Hyperparathyroidism. Lancet. 2009; 374:145-58. https://doi.org/10.1016/S0140-6736(09)60507-9
26. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JEM, Rejnmark L, *et al*. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporosis Int. 2017;28:1-19. https://doi.org/10.1007/s00198-016-3716-2
27. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. Lancet. 2018;391:168-78. https://doi.org/10.1016/S0140-6736(17)31430-7
28. Bilezikian JP. Primary hyperparathyroidism. J Clin Endocrinol Metab. 2018;103:3993-4004. https://doi.org/10.1210/jc.2018-01225
29. Herrero JA, López-Gómez JM, Maduell F, Martín-De Francisco AL, Martín-Malo A, Martínez-Castelao A, *et al*. Activación de los receptores de vitamina D en la optimización del hiperparatiroidismo secundario en diálisis. Nefrologia. 2013;33:571-84. https://doi.org/10.3265/Nefrologia.pre2013.May.11901
30. Ho LY, Wong PN, Sin HK, Wong YY, Lo KC, Chan SF, *et al*. Risk factors and clinical course of hungry bone syndrome after total parathyroidectomy in dialysis patients with secondary hyperparathyroidism. BMC Nephrol. 2017;18:12. https://doi.org/10.1186/s12882-016-0421-5
31. Jakubauskas M, Beiša V, Strupas K. Risk factors of developing the hungry bone syndrome after parathyroi-

dectomy for primary hyperparathyroidism. Acta Medica Litu. 2018;25:45-51. https://doi.org/10.6001/actamedica.v25i1.3703

32. Cohen MS, Dilley WG, Wells SA, Moley JF, Doherty GM, Sicard GA, *et al*. Long-term functionality of cryopreserved parathyroid autografts: A 13-year prospective analysis. Surgery. 2005;138:1033-41. https://doi.org/10.1016/j.surg.2005.09.029
33. Pitt SC, Sippel RS, Chen H. Secondary and tertiary hyperparathyroidism, state of the art surgical management. Surg Clin North Am. 2009;89:1227-39. https://doi.org/10.1016/j.suc.2009.06.011
34. Schlosser K, Zielke A, Rothmund M. Medical and surgical treatment for secondary and tertiary hyperparathyroidism. Scand J Surg. 2004;93:288-97. https://doi.org/10.1177/145749690409300407
35. Tominaga Y. Surgical treatment of secondary hyperparathyroidism due to chronic kidney disease. Ups J Med Sci. 2006;111:277-92. https://doi.org/10.3109/2000-1967-047