International Journal of **Health Science**

ASSOCIATION BETWE-EN PRIMARY HYPER-PARATHYROIDISM AND PARATHYROID GLAND ADENOMA

João Francisco Pozzebon Dotto
Graduation Student in medicine course by: ``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0008-7798-7479

Vinícius Freitas Pedron
Graduation Student in medicine course by: ``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0000-0002-9097-7960

Luiza Caffarate Sarturi
Graduation Student in medicine course by: ``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0000-0003-4675-5647

Pedro Caffarate Sarturi
Doctor graduated by: ``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0006-2123-5337

Luane Dornelles Loureiro
Graduation Student in medicine course by: ``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0006-2528-5905

Maria Elizabeth Bonorino Bortolanza
Graduation Student in medicine course by: ``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0001-9116-1533

Lucca Corcini Biscaino
Graduation Student in medicine course by:
``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0001-2651-6895

Gisre Merg Saraiva
Graduation Student in medicine course by:
``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0006-3999-2862

Lillian Cocco
Graduation Student in medicine course by:
``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0004-7947-0036

Luana Trindade dos Santos
Graduation Student in medicine course by:
``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0008-3702-5216

Elisa de Ávila Lopes
Graduation Student in medicine course by:
``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0001-1366-0214

Renata Cursano Hoch
Graduation Student in medicine course by:
``Universidade Franciscana ``(UFN)
Santa Maria, Rio Grande do Sul
ORCID: 0009-0000-1623-7422

Abstract: Primary hyperparathyroidism is an endocrinological disorder related to calcium metabolism. Typically, it is characterized by hypercalcemia and elevated serum concentrations of parathyroid hormone (PTH), the hormone produced by the parathyroid glands. Most cases of primary hyperparathyroidism occur due to an adenoma of the parathyroid glands (85% of cases). Biochemical screening tests, introduced in the 1970s, made it possible to diagnose the disease earlier, even in the asymptomatic phase. The disease can be diagnosed at a symptomatic stage, typically in countries where screening tests are not common. In the symptomatic phase, the disease can cause bone loss, kidney stone formation, as well as gastrointestinal, cardiovascular and neuropsychiatric manifestations. Primary hyperparathyroidism may present with serum calcium concentration within the normal range, but with parathyroid hormone at levels above the normal limit. Diagnosis of the disease involves clinical manifestations, laboratory tests and imaging tests, with ultrasound and 99mTc-sestamibi scintigraphy being the most commonly used imaging methods. The only treatment that can cure the disease is parathyroidectomy, in which one or more parathyroid glands are removed. Surgery allows an increase in bone mineral density and reduces the incidence of nephrolithiasis. For patients who do not undergo surgery, monitoring of serum calcium concentrations and bone mineral density is indicated.

Keywords: primary hyperparathyroidism, parathyroid hormone, parathyroid gland adenoma

INTRODUCTION

Primary hyperparathyroidism is the third most common endocrine disease (NILSSON, 2019). It is caused by the hypersecretion of parathyroid hormone (PTH) in one or more parathyroid glands (ALQAHTANI, et al, 2022). Typically, a single benign parathyroid adenoma is the cause of the pathology (BILEZIKIAN, et al., 2016).

The laboratory consequences of abnormally active parathyroid tissue are typically hypercalcemia and parathyroid hormone concentrations above the normal range or inadequately normal in the context of hypercalcemia (BILEZIKIAN, et al., 2018).

When primary hyperparathyroidism was first described, the disease was associated with severe hypercalcemia, as well as severe skeletal and renal complications. The indelible association of primary hyperparthyroidism with signs (kidney stones and fractures) and symptoms (due to hypercalcemia) persisted until the 1970s, when biochemical screening tests began to be routinely employed, first in the United States and then elsewhere (SILVA, et al, 2018).

The incidence of primary hyperparathyroidism increased markedly in countries where biochemical screening tests began to be used (BILEZIKIAN, et al., 2016). With the advent of routine calcium screening, the classic presentation of kidney and bone symptoms has largely been replaced by mild, asymptomatic disease (ZANOCCO, 2016). Thus, the typical diagnosis of primary hyperparathyroidism is no longer accompanied by evident skeletal and renal involvement (BILEZIKIAN, et al., 2018). However, asymptomatic individuals may still present evidence of complications and target organ involvement (BILEZIKIAN, et al., 2016).

Symptomatic primary hyperparathyroidism still occurs and may be the most prominent form of the disease in countries where biochemical screening tests are not routinely used (BILEZIKIAN, et al., 2016).

Diagnostic advances allow us to accurately measure parathyroid hormone (PTH) levels and image the parathyroid glands; Surgical techniques have also improved. Despite these advances and the availability of medical therapies that address some of the disease's complications, parathyroidectomy remains the only curative treatment.

LITERATURE REVIEW

EPIDEMIOLOGY

Primary hyperparathyroidism (PTPH) was characterized as a distinct clinical manifestation in 1920-1930. Since then, the epidemiology of the disease and clinical-investigative protocols have witnessed a significant change (YADAV, et al, 2020).

Before the 1970s, primary hyperparathyroidism was a rarely detected disease associated with notable morbidity (NILSSON, 2019). From the 1970s onwards, primary hyperparathyroidism became more routinely diagnosed, in an asymptomatic stage, due to increased screening (BILEZIKIAN, et al., 2016).

The incidence of primary hyperparathyroidism increased markedly in the United States in July 1974, when the serum calcium level was included in the research panel (MARCOCCI, 2011). The incidence declined in the US until 1998, when another sharp increase was observed, attributed to the introduction of osteoporosis screening guidelines and targeted testing in patients with osteoporosis (WALKER, 2018).

Primary hyperparathyroidism is the third most common endocrine disease, with an estimated prevalence of 0.1-0.4% (ALQAHTANI, et al, 2022). The prevalence of the disease in the United States has been estimated at 23 cases per 10,000 women and 8.5 per 10,000 men (INSOGNA, 2018).

The annual incidence of primary hyperparathyroidism is 65 per 100,000 women and 25 per 100,000 men (ZANOCCO, 2016). The peak incidence is reached in the seventh decade of life (MARCOCCI, 2011). Its incidence increases with age, with a predilection for females aged between 50 and 60 years (AL-QAHTANI, et al, 2022).

Women are affected twice as often as men, probably because the increase in bone resorption that follows menopause reveals hyperactivity of the parathyroid gland. Estrogen would have a modulating action on PTH secretion by the main parathyroid cells. During menopause, estrogen deficiency allows an increase in PTH secretion. The incidence of hyperparathyroidism, in studies, was higher among black individuals, followed by whites, Asians, Hispanics and others (YEH, et al, 2013).

In the USA and Canada, primary hyperparathyroidism predominantly presents as an asymptomatic disorder. Similar to the epidemiology in North America, hyperparathyroidism in Europe also presents as an asymptomatic disorder. In Asia, primary hyperparathyroidism is more likely to present with marked hypercalcemia and organ involvement than in other regions of the world. Hyperparathyroidism appears to be associated with presentation, that is, in countries where the prevalence is higher, primary hyperparathyroidism tends to be more asymptomatic (BILEZIKIAN, et al., 2018).

RISK FACTORS

The main risk factors for developing primary hyperparathyroidism include exposure to ionizing radiation, prolonged use of lithium and family history (ZANOCCO, 2016). Radiation, especially treatment in childhood, has been identified as a risk factor for the development of primary hyperparathyroidism (NILSSON, 2019).

In the presence of lithium, higher serum calcium concentrations are required to inhibit parathyroid hormone (PTH) secretion. It is postulated that this change results in sustained stimulation of the parathyroid tissue, leading to an increase in parathyroid volume and the possibility of adenomatous transformation (ZANOCCO, 2016).

The disease was more likely in patients whose calcium intake and physical activity were lower, and whose waist circumference and body weight were higher. Hypertension and use of loop diuretics, such as furosemide, also appear to be associated with a greater risk of developing primary hyperparathyroidism (BILEZIKIAN, et al., 2018).

ETIOLOGY

Primary hyperparathyroidism is classified as sporadic (90-95%) or familial hereditary (5-10%). In the sporadic type, solitary adenoma is the most prevalent cause (85%), followed by multiglandular parathyroid hyperplasia (10%) (ALQAHTANI, et al, 2022).

The pathology may be part of hereditary endocrine syndromes, including multiple endocrine neoplasia type 1 (MEN1), MEN2A, MEN4, hyperparathyroidism-hereditary jaw tumor syndrome, familial isolated hyperparathyroidism, familial hypocalciuric hypercalcemia (FHH) and severe neonatal hyperparathyroidism (BILEZIKIAN, et al., 2016). The familial hereditary type is usually caused by multiglandular parathyroid hyperplasia and multiple adenomas (ALQAHTANI, et al, 2022).

Parathyroid cancer is rare and constitutes less than 1% of all cases of primary hyperparathyroidism and about 0.005% of all cancers. It occurs alone or as part of a complex and hereditary syndrome (NILSSON, 2019).

PATHOPHYSIOLOGY

The parathyroid hormone (PTH) gene is located on chromosome 11 (Bilezikian JP et al., 2016). PTH was isolated in a pure form, being first synthesized in the ribosomes in the form of a pre-prohormone, a polypeptide chain of 110 amino acids. This form undergoes the first cleavage, transforming into a prohormone with 90 amino acids, and then into the hormone itself with 84 amino acids by the endoplasmic reticulum and Golgi complex; Finally, the hormone is stored in secretory granules in the cytoplasm of the cells (GUYTON, 2011).

Parathyroid hormone (PTH) can be secreted by exocytosis, degraded within secretory vesicles (producing fragments that are released into circulation) or sequestered in a stored pool. In healthy individuals, parathyroid hormone is released both with circadian dynamics and in a pulsatile manner, so that its dual anabolic and catabolic actions are well balanced (BILEZIKIAN, et al., 2016).

Physiologically, parathyroid hormone (PTH) increases bone reabsorption, increases renal calcium reabsorption and inhibits renal phosphate reabsorption. Furthermore, it promotes the synthesis of the active form of Vitamin D (1,25-dihydroxyvitamin D (1,25(OH)2D), which increases the absorption of calcium and phosphate in the intestine (Figure 3) (ALQAHTANI, et al, 2022).

The main regulators of parathyroid hormone (PTH) secretion are extracellular ionized calcium (Ca2+) and 1,25-dihydroxyvitamin D (1,25(OH)2D). Other potentially important regulators include serum phosphate and fibroblast growth factor 23 (FGF23) (BILEZIKIAN, et al., 2016).

Under normal conditions, an increase in the concentration of circulating ionized calcium, which may not be detected by biochemical methods, will lead to instantaneous suppression of parathyroid hormone secretion. Likewise, an imperceptible reduction in serum calcium concentration will immediately stimulate the secretion of parathyroid hormone. Parathyroid hormone increases the tubular formation of 1,25-dihydroxyvitamin D, therefore, an increase in parathyroid hormone determines an increase in 1,25-dihydroxyvitamin D. (BILEZIKIAN, et al., 2018).

The increase in serum phosphate levels indirectly stimulates the synthesis and secretion of parathyroid hormone (PTH), as well as the proliferation of parathyroid cells by binding to calcium, thus decreasing the serum calcium concentration (BILEZIKIAN, et al., 2016).

Fibroblast growth factor 23 (FGF23) suppresses PTH gene expression and protein secretion through a direct bone-parathyroid feedback loop, and may be an important modulator of PTH signaling (NILSSON, 2019).

The calcium-sensing receptor on parathyroid chief cells detects small changes in serum calcium. As a result, high levels of calcium block the production of PTH due to a negative feedback mechanism (ALQAHTANI, et al, 2022).

In primary hyperparathyroidism, parathyroid activity is abnormal (Saad M Alqahtani, et al). In this context, isolated parathyroid cells overproduce the hormone PTH, because they have lost their great sensitivity to serum calcium concentration (BILEZIKIAN, et al., 2018).

Due to the abnormal production of parathyroid hormone, there is an increase in renal absorption of calcium; of the synthesis of 1,25(OH)2D3, which stimulates the synthesis of the calbindin protein, in the intestinal mucosa, and promotes the absorption of calcium in the microvilli and bone reabsorption. The action of PTH, at the level of the renal tubule, will inhibit the reabsorption of phosphorus, causing phosphaturia (Figure 4) (ALQAHTANI, et al, 2022).

When patients with primary hyperparathyroidism develop hypercalciuria, the filtered calcium load is greater than the renal capacity to reabsorb calcium, because it exceeds its calcium reabsorption threshold efficiently, even under the influence of PTH (BILEZIKIAN, et al., 2016).

In primary hyperparathyroidism, there is an increase in chloremia and hydrogen concentration, due to the tubular action of PTH, as well as inhibition of tubular bicarbonate reabsorption, resulting in hyperchloremic acidosis (BILEZIKIAN, et al., 2016).
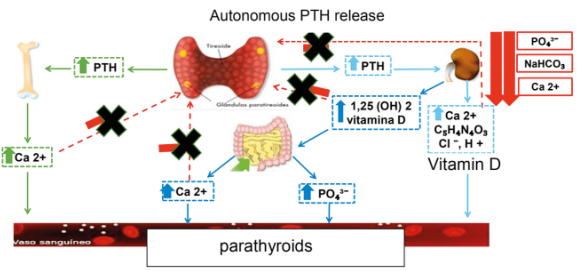
In patients with primary hyperparathyroidism, chronically elevated PTH levels lead to bone loss, mediated by receptor activation of nuclear factor κβ ligand (RANKL, also known as TNFSF11), osteoporosis (particularly in sites richer in cortical bone), and fractures. due to fragility (BILEZIKIAN, et al., 2016).

Constitutional mutations of the tumor suppressor genes MEN1 and CDC73 and the calcium receptor gene CASR are the most common variants in primary hyperparathyroidism. MEN1 mutations are observed in parathyroid adenomas, while CDC73 mutations occur in 70% of parathyroid carcinomas but only in about 2% of parathyroid adenomas (NILSSON, 2019).
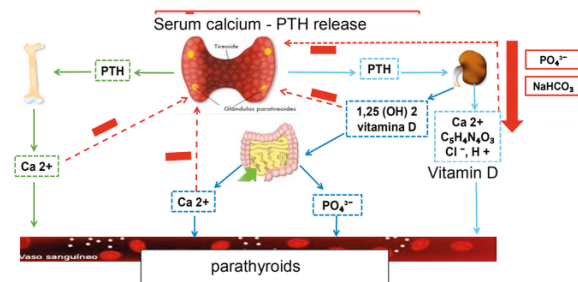
Figure 3: Physiology of Serum Calcium Regulation.

Picture elaborated by the author.

Figure 4: Pathophysiology of Primary Hyperparathyroidism.

Picture elaborated by the author.

CLINICAL PRESENTATION

The availability of automated serum screening panel has changed the clinical presentation of primary hyperparathyroidism. While before the 1970s, this was a disease of recurrent kidney stones, osteitis fibrosa cystica, neuromuscular dysfunction characterized by type II muscle cell atrophy, and symptomatic hypercalcemia, it has now become an asymptomatic or mildly symptomatic disease, detected by incidental finding. of hypercalcemia (FEDER, et al, 2011).

Primary hyperparathyroidism generally affects the kidneys and skeleton. Other systems, such as the gastrointestinal, cardiovascular and nervous systems, can also be affected. The bone diseases most commonly observed in primary hyperparathyroidism are osteoporosis and osteopenia (ALQAHTANI, et al, 2022).

In relation to the skeletal system, any combination of fragility fractures, skeletal deformities and bone pain is possible (SILVA, et al, 2018).

Fragility fractures, defined as fractures resulting from traumatic energy less than a fall from standing height, are the most common skeletal manifestations of primary hyperparathyroidism (ZANOCCO, 2016). Bone fracture is associated with muscle weakness, which usually affects the proximal part. This weakness is caused by atrophy of type II muscle fibers (ALQAHTANI, et al, 2022).

High rates of bone remodeling, in addition to impaired microarchitecture and bone quality, may contribute to the risk of fracture (INSOGNA, 2018). When the disease is advanced, cystic fibrous osteitis expresses the skeletal manifestations of primary hyperparathyroidism. This manifestation is typically characterized by bone pain, skeletal deformities and pathological fractures (BILEZIKIAN, et al., 2016).

On the other hand, in asymptomatic primary hyperparathyroidism, skeletal involvement is typically seen only by bone mineral densitometry (BMD), which shows a reduction, especially of the cortical bone compartment, best seen in the distal third of the radius (BILEZIKIAN, et al., 2016).

The incidence of classic renal involvement has decreased over the years, as the incidence of asymptomatic disease has increased (SILVA, et al, 2018). Primary hyperparathyroidism can occur with nephrolithiasis, nephrocalcinosis, renal colic, polyuria and renal failure (ALQAHTANI, et al, 2022). Currently, the most common complication of the disease is nephrolithiasis, affecting 15% to 20% of newly diagnosed patients. Most stones tend to be calcium oxalate; however, slightly alkaline urine may favor the precipitation of calcium phosphate stones (MACHADO, 2019).

Abdominal pain, nausea, vomiting, pancreatitis, peptic ulcers, and constipation are gastrointestinal manifestations of primary hyperparathyroidism. Hypergastrinemia and decreased neuromuscular excitability cause pancreatitis and peptic ulcers (ALQAHTANI, et al, 2022).

Lethargy, depressed mood, psychosis, decreased social interaction, as well as cognitive dysfunction are also symptoms related to primary hyperparathyroidism (MACHADO, 2019).

Insulin resistance associated with hyperglycemia and dyslipidemia (decreased cholesterol levels, high-density lipoprotein cholesterol levels, and increased total triglyceride levels) have been reported, but it remains unclear how often these are attributable to hyperparathyroidism, and whether they are improved. by surgery (MARCOCCI, 2011).

Different studies have reported cardiovascular manifestations, including hypertension, atherosclerosis, myocardial and valvular calcification, endothelial dysfunction, left ventricular hypertrophy, shortened QT interval, bradycardia, heart block, arrhythmias, coronary artery diseases and lipid abnormalities (ALQAHTANI, et al, 2022).

DIAGNOSIS

The diagnosis of primary hyperparathyroidism is biochemical, and based on a high concentration of Ca,2, + in combination with elevated or inappropriately "normal" levels of parathyroid hormone (PTH). The individual assessment of patients with primary hyperparathyroidism must always be based on a safe diagnosis and the exclusion of differential diagnoses (NILSSON, 2019).

The finding of hypercalcemia in routine biochemical examinations or, in the evaluation of postmenopausal women with osteoporosis, is typically the initial clue for the diagnosis of primary hyperparathyroidism (MARCOCCI, 2011).

Approximately 50% of circulating calcium is free (Ca2+). The remainder is mainly linked to albumin. Measuring ionic Ca^2+ more accurately reflects true calcium and must be preferred if available, but is sensitive to changes in pH levels. The total calcium measurement must be corrected for serum albumin by 0.2 mmol/L for every 10 g/L (0.8 mg for every 1 g) where serum albumin is below 40 g/L (4g). Around 40% of patients with primary hyperparathyroidism

have normal serum phosphorus levels, due to the richness of phosphorus in the diet. Serum phosphorus levels below 2.5 mg/dl, associated with hypercalcemia, are suggestive of hyperparathyroidism. When hypercalcemia and hypophosphatemia occur, with phosphorus values below 2.2 mg/dl, there is a strong probability of primary hyperparathyroidism. (NILSSON, 2019).

The many technical issues related to direct measurement of ionized calcium lead many experts to recommend adjusted total calcium as the best way to assess serum calcium concentration. It is useful to repeat serum calcium measurements several times over a period of 3 to 6 months due to pulses of secretion that occur in endocrine adenomas. (BILEZIKIAN, et al., 2016).

Measuring serum PTH is the next step in evaluating hypercalcemia. A low or undetectable PTH level excludes primary hyperparathyroidism and raises the possibility of cancer-associated hypercalcemia. If the PTH level is elevated in a person with a known malignancy, the most likely diagnosis is concomitant primary hyperparathyroidism; Ectopic production of PTH from a tumor is extremely rare (MARCOCCI, 2011).

In primary hyperparathyroidism, serum PTH levels may be markedly increased or in the normal range. However, a "normal" PTH value in someone with hypercalcemia is clearly not a normal physiological value (BILEZIKIAN, et al., 2016).

The finding of a normal albumin-adjusted or ionized serum calcium level and an elevated PTH level in patients with no other causes of secondary hyperparathyroidism is consistent with normocalcemic primary hyperparathyroidism (MARCOCCI, 2011). In normocalcemic primary hyperparathyroidism, serum albumin-corrected calcium and ionized calcium levels are persistently normal in the presence of elevated PTH levels. Furthermore,

kidney function, vitamin D level and urinary calcium excretion are all within normal limits (ALQAHTANI, et al, 2022).

Bone resorption inhibitors, such as bisphosphonates and denosumab, generally cause an increase in serum PTH concentrations, making the diagnosis of normocalcemic primary hyperparathyroidism in these conditions uncertain (BILEZIKIAN, et al., 2016).

Diagnostic laboratory tests must include serum phosphate measurements, renal function tests, and serum 25-hydroxyvitamin D measurements. The 24-hour urinary calcium level must also be measured and, if > 400 mg per day, a complete analysis of the stone risk profile must also be evaluated (BILEZIKIAN, et al., 2016). Serum phosphorus concentration is typically at the lower end of the normal range, between 0.97 and 1.13 mmol/L (BILEZIKIAN, et al., 2018).

Primary hyperparathyroidism is associated with increased bone remodeling and an increased incidence of fractures (NILSSON, 2019). The classic pattern of skeletal involvement shown on bone mineral densitometry is the greatest reduction in the distal third of the radius, a cortical site, followed by lesser degrees of involvement in the hip and lumbar spine regions, endowed with a greater proportion of trabecular bone (BILEZIKIAN, et al., 2018).

As for preoperative localization methods, there are two types of methods: invasive and non-invasive. Non-invasive methods include cervical ultrasound, four-dimensional computed tomography (4D-CT), 99mTc-sestamibi scintigraphy, single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and positron emission tomography combined with computed tomography (PET/CT). Fine needle aspiration (FNA), selective venous sampling and selective arteriography are useful invasive methods in re-operative cases (ALQAHTANI, et al, 2022).

The most common preoperative localization imaging techniques used in primary hyperparathyroidism are 99mTc-sestamibi scintigraphy and ultrasound (ALQAHTANI, et al, 2022).

Single-photon emission CT with technetium-99-labeled sestamibi identifies up to 89% of single parathyroid adenomas. Technetium-labeled sestamibi (99mTc MIBI) is absorbed by parathyroid and thyroid tissue. Uptake is increased and prolonged in adenomatous and hyperplastic parathyroids (FEDER, et al, 2011). The main advantage of sestamibi scanning is that it can localize ectopic parathyroid glands (MARCOCCI, 2011).

Ultrasonography is the second most useful modality and, when used with 99mTc MIBI preoperatively, can increase adenoma detection rates (FEDER, et al, 2011). It is a simple, cheap and effective method to detect enlarged cervical parathyroid glands. It can be done both preoperatively and intraoperatively, and there is no risk of exposure to radiation. However, it has limitations in locating a parathyroid adenoma in the retroesophageal region, tracheoesophageal groove, intrathyroidal, mediastinum or other ectopic locations. Furthermore, it is less effective in cases of multinodular goiter and lesions smaller than 5 mm (ALQAHTANI, et al, 2022).

Plain radiography of the skeleton is not recommended, except in rare cases of severe disease, in which cystic fibrous osteitis is suspected (MARCOCCI, 2011).

Simple computed tomography and magnetic resonance imaging are less useful, except in the context of persistent or ectopic production (FEDER, et al, 2011).

In young patients with primary hyperparathyroidism (<30 years of age), those with multiglandular disease, family history (affected first-degree relatives), or those with parathyroid cancer, specific genetic testing may be necessary (BILEZIKIAN, et al., 2016).

TREATMENT

Patients who do not meet surgical criteria or those who refuse surgery must be monitored for signs of disease progression (BILEZIKIAN, et al., 2016). This includes measurement of serum calcium, serum creatinine level, and estimated glomerular filtration rate annually. In addition, bone density (hip, spine and forearm) must be measured every one to two years. If there is a history of nephrolithiasis or prevalent kidney stones, annual abdominal imaging tests (radiography, US or CT) and a 24-hour urine biochemical profile are recommended (ALQAHTANI, et al, 2022).

In addition, patients who are not candidates for surgery must have a calcium-sufficient diet (1,000 to 1,200 mg per day) and maintain a serum 25-hydroxyvitamin D level in the range of 20 to 30 ng per milliliter, with the use of vitamin supplements. D, as needed. Hydration is important to prevent worsening of hypercalcemia and reduce the risk of nephrolithiasis (INSOGNA, 2018).

Cinacalcet, a calcimimetic often used to lower serum PTH levels in secondary hyperparathyroidism, is approved by the U.S. Food and Drug Administration for the treatment of hypercalcemia in patients with parathyroid carcinoma and primary hyperparathyroidism who cannot undergo parathyroidectomy (BILEZIKIAN, et al., 2018).

Cinacalcet binds to regions of the calcium-sensitive receptor complex, thereby increasing sensitivity to calcium concentration. The calcium signal amplified by cinacalcet is transmitted to the parathyroid cell and thus reduces the synthesis and secretion of PTH. Continued use of cinacalcet for up to 5 years provides long-term control of serum calcium concentration. Furthermore, cinacalcet does not appear to have any effect on bone mineral density (BILEZIKIAN, et al., 2018).

The intravenous bisphosphonates ibandronate, pamidronate and zoledronic acid are used to inhibit bone resorption (ZANOCCO, 2016). The use of the bisphosphonate alendronate has also been studied in primary hyperparathyroidism. In contrast to cinacalcet, serum calcium concentration does not change, but bone mineral density improves, particularly in the lumbar spine, in both women and men (BILEZIKIAN, et al., 2018).

The use of denosumab, an inhibitor of the nuclear factor Kappa B activator ligand receptor, is an interesting approach, because it inhibits an important pathway in the catabolic actions of parathyroid hormone (BILEZIKIAN, et al., 2018).

Parathyroidectomy is the only definitive treatment for primary hyperparathyroidism (Nilsson, 2019). When this intervention is indicated, the objective is to cure the disease by removing the abnormal parathyroid tissue (MARCOCCI, 2011).

Guidelines from the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism suggest surgical intervention as opposed to observation in patients who meet one of the following criteria: serum calcium concentration of 1.0 mg/dL (0.25 mmol/L) or greater- above the upper limit of normality; bone density at the hip, lumbar spine, or distal radius greater than 2.5 standard deviations below peak bone mass; previous asymptomatic vertebral fracture; estimated glomerular filtration rate <60 mL/min; 24-hour urinary calcium > 400 mg/day (> 10 mmol/day); nephrolithiasis or nephrocalcinosis evidenced by radiography, ultrasound or CT; age under 50 years. (REIS, et al, 2022)

Parathyroidectomy is associated with a cure rate of 95 to 98% and a low rate (1 to 3%) of complications (laryngeal nerve paralysis and, less frequently, postoperative hypocalcemia) (MARCOCCI, 2011).

Surgical approaches to parathyroidectomy include bilateral cervical exploration and minimally invasive parathyroidectomy (MIP). The former is the standard procedure and has several advantages, including better inspection of all parathyroid glands, reduced morbidity, and prompt management of various presentations such as hyperplasia, supernumerary glands, double adenomas, and ectopic glands. MIP, on the other hand, employs a variety of techniques, such as robotic, radio-guided, video-assisted, endoscopic and focused mini-lateral incision (ALQAHTANI, et al, 2022).

Intraoperative PTH monitoring may be helpful; A 50% or greater decrease in the PTH level 10 minutes after adenoma resection compared with the highest value before excision suggests that all hyperfunctioning parathyroid tissue has been removed. Histological analysis usually shows a single benign chief cell adenoma (MARCOCCI, 2011).

Recurrence is rare in sporadic primary hyperparathyroidism, but the risk is greater in familial cases unless total parathyroidectomy is performed. Successful surgery is followed by an immediate normalization of the PTH level and serum and urinary calcium levels and gradual increases in bone mineral density (up to 10%), particularly during the first few years postoperatively in the lumbar spine and hip and, posteriorly, in the distal radius (MARCOCCI, 2011).

CONCLUSION

Primary hyperparathyroidism due to parathyroid adenoma is a common disease in the population. The main cause of this pathology is a single parathyroid gland adenoma. In recent decades, the majority of patients with this pathology have been asymptomatic, with the diagnosis being made through laboratory screening tests. Parathyroidectomy is the only definitive

treatment for primary hyperparathyroidism. Parathyroid hormone (PTH), serum and urinary calcium levels normalize immediately after the surgical procedure. Bone mineral density recovers completely in the first few years after surgery.

History taking and physical examination are essential to establish an early diagnosis. A high index of suspicion must be maintained in symptomatic patients, especially when there is musculoskeletal, renal, cardiovascular or gastrointestinal involvement. The symptoms of the disease can be severe to the point of compromising the daily life activities of patients with the disease, and early diagnosis is essential to preserve patients' functionality and quality of life.

REFERENCES

1. Bilezikian, J., Bandeira, L. et al. **Hyperparathyroidism**. Lancet, London, v. 391, n. 10116, p. 168-178, 2018.

2. Bilezikian, J., Cusano, N., Khan, A. et al. **Hiperparatireoidismo primário**. Nat Rev Dis Primers 2, 16033 (2016). https://doi.org/10.1038/nrdp.2016.33

3. Guyton, A.C. e Hall J.E.- **Tratado de Fisiologia Médica**. Editora Elsevier. 11ª ed., 2006.

4. Insogna, K. L. **Primary Hyperparathyroidism**. New England Journal of Medicine, Boston, v. 379, n. 11, p. 1050-1059, 2018

5. Jessica MacKenzie-Feder, Sandra Sirrs, Donald Anderson, Jibran Sharif, Aneal Khan, **"Hiperparatireoidismo primário: uma visão geral"**, International Journal of Endocrinology, vol. 2011, Artigo ID 251410, 8 páginas, 2011

6. Marcocci, C.; Cetani, F. **Primary Hyperparathyroidism**. New England Journal of Medicine, Boston, v. 365, n. 25, p. 2389-2397, 2011.

7. Nilsson I. L. **Primary hyperparathyroidism: must surgery be performed on all patients?** Current evidence and residual uncertainties (Review). J Intern Med 2019; 285: 149–164.

8. Reis, A. H., Bonifácio, F. P. et al. **Hiperparatireoidismo primário: uma revisão da literatura.** Brazilian Journal of Development, Curitiba, v.8, n.5, p.42281-42290, may., 2022

9. Saad M Alqahtani, **Primary Hyperparathyroidism: Review on Pathogenesis, Diagnosis, and Management**, J Res Med Dent Sci, 2022, 10(1): 210-215

10. Silva, B. C. et al. **Primary hyperparathyroidism**. Best Practice & Research Clinical Endocrinology & Metabolism, 2018, 32(5): 593-607.

11. Walker, M., Silverberg, S. **Hiperparatireoidismo primário**. Nat Rev Endocrinol 14, 115-125 (2018). https://doi.org/10.1038/nrendo.2017.104

12. Yadav, S., Johri, G. et al. **Primary hyperparathyroidism in developing world: a systematic review on the changing clinical profile of the disease.** Arch Endocrinol Metab. 2020;64/2

13. Yeh MW, Ituarte PH, Zhou HC, et al. **Incidence and prevalence of primary hyperparathyroidism in a racially mixed population**. J Clin Endocrinol Metab 2013; 98: 1122.

14. Zanocco, K. A.; Yeh, M. W. Primary **Hyperparathyroidism: Effects on Bone Health.** Endocrinol Metab Clin N Am, 2017, 46(1): 87–104