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Current Approaches in the Diagnosis and Treatment of Primary Hyperparathyroidism

INVITED REVIEW
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ABSTRACT

Primary hyperparathyroidism (pHPT) is a prevalent endocrine disorder. Recently, the diagnosis and treatment of the disease have undergone modifications. The autonomous synthesis of parathyroid hormone (PTH) by the parathyroid glands, which are essential for calcium metabolism, is the defining feature of this condition, which is crucial for calcium metabolism. Biochemical testing is used to make the diagnosis. The cure is also biochemically validated. Recently, there has been a notable rise in the occurrence of diseases as a result of the implementation of regular serum calcium screening. In addition to biochemical observations such as hypercalcemia and elevated levels of PTH, manifestations associated with the impairment of target organs were frequently observed in the past. Presently, a normocalcemic variety of the disease exists in terms of its biochemical characteristics, and it manifests as both symptomatic and asymptomatic clinical phenotypes. Hence, the ongoing progression of diagnostic and therapeutic approaches in the field of disease management persists. This review aims to provide an overview of contemporary methodologies utilized in the diagnosis and treatment of pHPT.

Keywords: Parathyroid adenoma, parathyroidectomy, primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (pHPT) is when the parathyroid glands make too much parathormone (PTH), which causes too much calcium in the body. The reported incidence and prevalence values of pHPT are quite inconsistent. The inconsistency is due to variations in healthcare systems.

Primary hyperparathyroidism diagnosis is exclusively dependent on biochemical markers. Imaging is not useful for making a diagnosis. The use of automated biochemistry panels to measure serum calcium has led to increased incidence and prevalence in countries with routine screening.[1-5] The prevalence rates for women and men in the United States are 233 and 85 per hundred thousand, respectively.[2] In India, where routine calcium screening is not performed, the prevalence is lower.[6] Recently, an increase in prevalence rates in China, where calcium is included in routine screenings, highlights the impact of healthcare systems on prevalence.[7-9] However, the incidence of the disease also varies according to age, sex, and race.[6] Women have a higher risk than men, approximately 3-4 times higher.[6] The higher prevalence in females can be attributed to the diagnosis of the disease, which was unmasked during the investigation of osteoporosis caused by estrogen deficiency.[10] The condition is more common in elderly people, particularly those in their fourth to sixth decades. Familial, genetic based cases may be detected in childhood.[10] Epidemiological studies, on the other hand, reveal that the white race is more risky than the black race.[2] As a result, prevalence varies according to age, gender, race, and country of residence.

Pathophysiology

Parathyroid glands secrete PTH, which plays a crucial role in calcium homeostasis. Parathormone acts as a defense mechanism against hypocalcemia. Cell-surface calcium-sensitive receptors (CaSRs) are the main factors that stimulate PTH. In pHPT, the decreased expression of CaSR results in an increase in parathyroid gene expression. This leads to the clonal growth of parathyroid glands and excessive secretion of PTH. The increased PTH exerts its hypercalcemia effect mainly through 3 target organs: the kidneys, bones, and intestine. Renal calcium excretion is reduced. Resorptive activity in bones increases. The production of 1,25$(OH)_2$D vitamin increases secondary to the increase of 1-alpha hydroxylase activity in

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the proximal tubules of the kidneys. Therefore, there is an increase in calcium absorption from the intestines. Ultimately, the elevation of the calcium load causes both hypercalcemia and hypercalciuria. Hypercalciuria can result in nephrocalcinosis and nephrolithiasis. There may also be a decrease in bone mineral density due to increased bone resorption (Figure 1).

Etiology

Primary hyperparathyroidism may occur due to an adenoma, hyperplasia, or cancer developing on the basis of genetic or environmental predisposing factors. The disease is usually sporadic. The genetic background is present in about 10% of all cases. It is estimated that in cases of genetic hyperparathyroidism, a mutation is present in approximately one of 10 genes that are considered to be responsible.[11,12] Multiple endocrine neoplasia (MEN) type 1, MEN 2A, MEN 4, hyperparathyroidism-jaw tumor syndrome, and familial isolated hyperparathyroidism are examples of genetic predisposing factors. Environmental factors can be listed as external radiation exposure,[13] radioactive iodine treatment,[14] thiazide diuretics, and lithium use.

The histopathological background of sporadic pHPT mostly involves single-gland adenomas (85%), less frequently multiglandular disease (MGD) (15%) and rarely (<1%) parathyroid cancer.[6,15] Understanding the underlying cause can guide management. For example, patients with pHPT, which developed as a manifestation of MEN syndrome, are more likely to have MGD. This is a contraindication for selective parathyroidectomy. Likewise, in a pHPT caused by hyperparathyroi dism–jaw tumor syndrome, bilateral neck exploration (BNE) should be planned, and the timing of parathyroidectomy should not be delayed due to the high risk of malignancy (10%-15%). On the other hand, if the presence of a single-gland adenoma is confirmed by preoperative imaging, selective parathyroidectomy would be an appropriate strategic approach.

Diagnosis and Classification

Prior to utilizing serum calcium levels for screening, pHPT diagnosed manifestations associated with target organs. This form of pHPT, now described as "symptomatic hypercalcemic primary hyperparathyroidism," represented the only biochemical and clinical form of the disease. However, with routine screening of calcium, diagnosing pHPT in patients who were examined for a cause unrelated to pHPT gave rise to the clinical concept of "asymptomatic pHPT." On the other hand, pHPT, which is diagnosed by performing routine PTH tests for the etiology in patients with osteoporosis but without hypercalcemia, has revealed the concept of "normocalcemic hyperparathyroidism."[16] There are currently 2 biochemical forms of the disease, hypercalcemic and normocalcemic pHPT, as well as 2 different clinical phenotypes, symptomatic and asymptomatic pHPT. The disease may be symptomatic or asymptomatic, regardless of the hypercalcemic or normocalcemic variant. Similarly, in the asymptomatic pHPT, there may or may not be target organ involvement, regardless of the presence of symptoms. Detection of target organ involvements such as nephrolithiasis or osteoporosis in the scans performed after the diagnosis of pHPT in a patient who was examined for an unrelated reason does not reclassify these patients as symptomatic. It would be more appropriate to use the term "asymptomatic pHPT with target organ involvement" for this patient.

Biochemical parameters used in the diagnosis of pHPT can show a dynamic course. Depending on the biochemical variants of the disease, various results can be obtained during the measurement period. For example, in the classical form of pHPT, elevated PTH levels are observed along with high total calcium levels. However, in the presence of hypercalcemia, a normohormonal variant in which PTH is inappropriately normal can also be observed. In the normocalcemic form, total and ionized calcium levels are normal, and high PTH levels are present. Moreover, these variants, which present biochemically various profiles, may present themselves in different ways. For example, it has been reported that 2 out of 3 patients followed up with a diagnosis of normohormonal pHPT and 3 out of 4 patients followed up with a diagnosis of hypercalcemic pHPT may have normal or milder biochemical parameters if measurements are made at different times.[17] Due to the various dynamic courses of biochemical parameters, sequential measurements are recommended.

According to the international guideline recommendations by the pHPT study group, for hypercalcemic pHPT, the presence of elevated or inappropriately normal PTH levels associated with elevated albumin-adjusted total calcium levels measured at least 2 weeks apart is diagnostic.[18] For normocalcemic variants, after exclusion of secondary hyperparathyroidism causes, high PTH levels accompanying normal total and ionized calcium levels in at least 2 different measurements with 3-6 month intervals are diagnostic.[18] When calculating total calcium levels, it is recommended to make adjustments for albumin levels (corrected calcium = serum calcium + 0.8 × [4 − serum albumin]).

Differential Diagnosis

Currently, the only curative treatment for pHPT is surgery. The goal of surgical treatment is to excise the abnormal parathyroid glands. In this respect, it is also crucial to screen for target organ involvement that will constitute a surgical indication as well as biochemical parameters. The primary target organs affected by the disease are the kidneys and bones. In addition, non-target organ involvement characterized by gastrointestinal, cardiovascular, and neurocognitive symptoms can also be observed. Table 1 shows the recommended tests in pHPT.

The baseline parameters to be examined in pHPT are mainly focused on target organ involvement. These parameters are generally common to both surgical and internal guidelines.[18,19] However, non-target

MAIN POINTS

- Primary hyperparathyroidism (pHPT) may occur due to an adenoma, hyperplasia, or cancer developing on the basis of genetic or environmental predisposing factors.
- At present, pHPT manifests in 2 biochemical forms: normocalcemic and hypercalcemic pHPT. Additionally, it manifests in 2 distinct clinical phenotypes: symptomatic and asymptomatic pHPT.
- Primary hyperparathyroidism can be diagnosed through biochemical measures. The use of imaging in diagnosis is useless.
- Surgery is the only effective treatment for pHPT. To choose a surgical course of action, one needs to carefully consider the disease's origin.
- Although the use of ablation techniques in treatment has started, the outcomes in the long run are unknown.

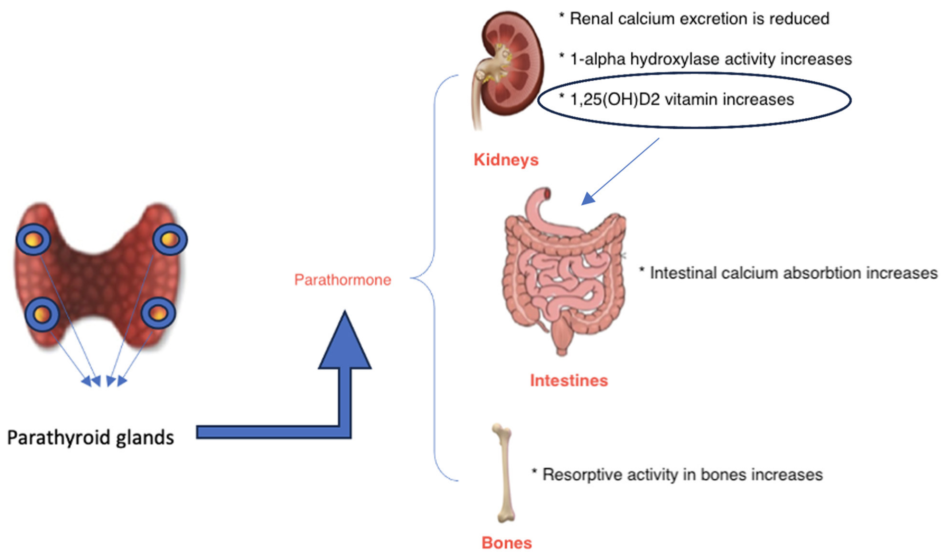

Figure 1. Pathophysiology of hyperparathyroidism.

organ involvement may also occur in pHPT. This is where the main differences between the guidelines emerge. In surgical guidelines, the presence of non-target organ involvement constitutes a relative indication for surgery. Therefore, it is routinely recommended to investigate non-target organ involvement in pHPT.[19] In the recently published parathyroid study group recommendations, non-target organ involvements do not constitute an indication for surgery. Therefore, they are not recommended to be routinely investigated.[18]

Another issue to be considered in pHPT is genetic examinations. Routine genetic screening is not recommended. However, genetic examination should be considered in the presence of a pHPT developed on the basis of MEN, pHPT, jaw tumor syndrome, or for patients younger than 30 years of age.

Management of Hyperparathyroidism

In patients with suspected pHPT, biochemical and radiological examinations should be performed to confirm the management of the disease. Biochemically, serum PTH, albumin, calcium (ionized calcium for normocalcemic hyperparathyroidism), vitamin D, and creatine levels should be measured. As for imaging methods, vertebral x-rays or bone densitometry can be used as indicators of bone involvement. Glomerular filtration rate and 24-hour urine calcium should be measured to detect renal involvement. Besides, urinary ultrasound or computed tomography may be performed for nephrolithiasis or nephrocalcinosis. Preoperative parathyroid imaging has no diagnostic value. Parathyroid imaging can be performed to localize diseased glands in patients undergoing surgery. For patients who have an indication for surgery but do not want to undergo surgery, medical treatments can be applied to prevent the development of disease-related complications. The main goal of medical treatment is to reduce high serum calcium levels and increase bone mineral density. Accordingly, cinacalcet can be used to decrease serum calcium. There is no need for calcium restriction in the diet. Calcium needs can be adjusted according to the Institute of Medicine nutritional guidelines. In this context, daily calcium intake can be planned as 800 mg/day for women younger than 50 years of age and men younger than 70 years of age and 1000 mg/day for women older than 50 years of age and men older than 70 years of age. The vitamin D level should be adjusted to be higher than 30 ng/mL and lower than the laboratory upper limit. Bisphosphonates, or denosumab, may be used to increase bone mineral density.

Bisphosphonates or denosumab may be considered in combination with cinacalcet to decrease serum calcium and increase bone mineral density.

Table 1. Evaluation of the Patient with Primary Hyperparathyroidism

Biochemical	Bones	Kidneys
Total calcium	Vertebral x-ray	GFR, creatine clearance
Ionized calcium*	Bone densitometry	24-hour urinary calcium
Albumin		Urinary system imaging**
PTH		
Vitamin D		
Creatine		

GFR, glomerular filtration rate; PTH, parathormone.
*Not required in the routine. If a normocalcemic variant is considered, it should be examined.
**Direct urinary system radiography, ultrasonography, or tomography can be preferred for nephrolithiasis and nephrocalcinosis.

Surgical Indications

Indications for parathyroid surgery were generally determined by observational studies that examined symptomatic regression and the risk of complications in patients who had undergone parathyroidectomy.

Patients younger than 50 years of age require long-term follow-up. In addition, patients with an albumin-adjusted total calcium level higher than 1 mg/dL above the upper limit of normal are more likely to have disease progression.[20] Moreover, there are reports of improvements in parameters related to target organ involvement after successful parathyroidectomy.[21-24] The achievement of normocalcemia significantly decreases the risk of nephrolithiasis.[21] Although nephrocalcinosis does not regress, renal functions are more stable, especially in patients with a GFR <60 mL/min. Although there are contradictions about the improvement in fracture risk, it is clear that there is an increase in bone mineral density after parathyroidectomy.[22] Therefore, the most effective treatment method today is parathyroidectomy for patients with target organ involvement and a high risk of complications. Both follow-up and pharmacological treatment are more costly and less effective than surgery.[25] Indications for surgery in line with the latest guideline published in 2022 by the pHPT study group are given in Table 2.

Although surgical indications differ between guidelines, they have evolved over time to mainly include patients with target organ involvement and an increased risk group. Table 2 shows common indications in different guidelines. However, some changes were made to these common indications in the 2022 guidelines of the parathyroid study group.[18] The first of these changes is that, while determining the indication for parathyroidectomy in patients with a single kidney, values higher than 60 mL/min in the glomerular filtration rate can be taken as a basis. Secondly, different threshold values were determined according to gender for 24-hour urinary calcium levels, which were previously determined as >400 mg/day. In this respect, levels of >250 mg/day in women and >300 mg/day in men in a 24-hour urinary calcium measurement constitute a surgical indication. The last change is related to bone densitometry measurements. While any *T* score < −2.5 continues to be an indication for surgery, this indication has been partially expanded. This expansion has been updated to suggest that the *Z* score can be used instead of the *T* score in bone densitometry measurements in premenopausal women and men under 50 years of age.[18]

The effects of a successful parathyroidectomy on complications and symptoms related to target organ involvement are clear. However, the role of surgical treatment in non-target organ involvement is still controversial. There is no doubt that pHPT can be associated with manifestations of non-target organ involvement, such as neurocognitive, cardiovascular, and gastrointestinal symptoms. However, the results of the studies examining the effects of parathyroidectomy on these symptoms, which are generally subjective, are contradictory. Moreover, most of the studies are observational, and the level of evidence is low. In the psychiatric and surgical literature, there are studies reporting the positive effects of parathyroidectomy on neurocognitive symptoms.[26-30] Accordingly, neurocognitive symptoms presumed to be associated with pHPT are accepted as a relative surgical indication.[19,31] However, it was emphasized that parathyroidectomy did not show consistent effects on neurocognitive symptoms in a prospective randomized controlled study with a 10-year follow-up period published by Pretorius et al.[32]

As mentioned above, the diagnosis of pHPT is based on biochemical parameters. Imaging has no place in diagnosis. The most effective treatment method is surgery. Therefore, after diagnosis, patients should be evaluated for surgical indications. Regardless of the presence of symptoms, parathyroidectomy has better outcomes than medical therapy for patients who meet the criteria in Table 2. Moreover, surgical treatment continues to be an option for patients who do not meet surgical indications and are thought to have follow-up problems. Patients should be referred to surgeons experienced in parathyroid diseases. The definition of an experienced parathyroid surgeon differs between guidelines.[18,19] Some guidelines say 10 per year; some guidelines consider surgeons who perform more than 50 parathyroid surgeries per year as experienced.[18,19] Although the numbers vary, the fact that the surgeries have lower complication rates in the hands of experienced surgeons does not change.[33-35]

Preoperative Localization Studies

After the diagnosis is confirmed, the treatment approach should basically be shaped by how the operative strategy will be established. At this stage, the role of preoperative imaging becomes crucial. Although it has no role in diagnosis, preoperative imaging is an important element in determining the surgical approach. Options such as ultrasonography (USG), scintigraphy, 4-dimensional computed tomography (4D-CT), 4-dimensional magnetic resonance imaging (4D-MRI), and positron emission tomography (PET) are available as preoperative imaging modalities. Ultrasonography is an easy-to-access and cost-effective imaging method. However, concomitant thyroid pathology is found in 12%-67% of patients with pHPT.[19] In addition, considering that it allows PTH washout, especially in reoperative parathyroidectomies, USG is generally the first preferred imaging method.[36] On the other hand, being practitioner dependent and less effective with obese patients can be counted as a disadvantage of USG.[37,38] Various results have been reported in studies examining the effectiveness of USG in parathyroid imaging, as there are many factors affecting its sensitivity. In the meta-analysis where Agha et al[39] investigated the effectiveness of USG in parathyroid imaging, the sensitivity was reported as 76.1%. The authors also stated that higher sensitivity values can be obtained by using contrast-enhanced USG.[40]

Another commonly used test in preoperative imaging is scintigraphy. Parathyroid tissue contains oxyphil cells rich in mitochondria. The sensitivity of scintigraphy increased with the use of technetium 99m (Tc 99m) sestamibi, which is particularly involved in these cells.[41] Technetium 99m sestamibi is retained in the thyroid tissue as well as in the parathyroid. However, sestamibi washout is slower in parathyroid adenomas than in normal parathyroid and thyroid tissues.[42] Diseased glands can be localized with dual-phase imaging, which is developed by taking advantage of this feature. However, the presence of a thyroid nodule that may cause delayed washout of sestamibi may cause false-positive results.[43] In addition, it is known that false-negative results increase in the presence of a small adenoma or

Table 2. Surgical Indications in Primary Hyperparathyroidism

Those with Target Organ Involvement		Those at Increased Risk of Complications
Kidneys	Bones	
GFR < 60 mL/min	Vertebral fracture	Age <50 years
High 24-hour urinary calcium*	Any *T* score < −2.5 on bone densitometry	Calcium level higher than 1 mg/dL above the upper limit of normal
Nephrolithiasis, nephrocalcinosis		

GFR, glomerular filtration rate.
**>250 mg/day in women, >300 mg/day in men.

hyperplasia, so the sensitivity of scintigraphy decreases.[44] In general, the sensitivity of sestamibi scintigraphy in single-gland adenomas is 85%-90%, and this value decreases to 45%-50% in the presence of MGD.[44] However, it has been shown that combining sestamibi with USG increases the sensitivity of determining localization.[45] This situation has made the combination of USG and sestamibi the first preferred method as a preoperative imaging method in many centers today.

Another imaging modality that has recently gained popularity is 4D-CT.[19] Similar to USG, classical tomography offers sections in transverse, sagittal, and coronal dimensions. Therefore, classical tomography has no additional contribution compared to the combination of USG and sestamibi in imaging. However, in 4D-CT, which is a dynamic imaging method, fourth-dimensional cross-sections, including images of the uptake of the contrast agent in the arterial and venous phases, are obtained.[43,46] The sensitivity of 4D-CT in primary operations was reported to be 89.4%, and its contribution is marginal when compared to the combination of USG and sestamibi.[47] In addition, the sensitivity of 4D-CT decreases in the presence of MGD similar to the combination of USG and sestamibi.[19] However, 4D-CT shows better results in patients for whom the USG + sestamibi combination is negative or incompatible.[48-50] Similarly, there are reports showing that 4D-CT is superior to USG + sestamibi in reoperative parathyroidectomies.[47] The main obstacle for 4D-CT to be the primary imaging method is that it creates radiation exposure and requires an experienced radiologist.[47] Therefore, 4D-CT is generally used in tertiary centers today and is preferred in cases of negative or inconsistent USG + sestamibi or in reoperative parathyroidectomy.

Another examination used as a preoperative localization study is 4D-MRI. Its sensitivity is similar to the combination of USG and sestamibi, and it is advantageous over 4D-CT because it does not cause radiation exposure. However, artifacts caused by patient movements due to the long exposure time are the most important problem limiting radiological evaluation.[51] Although it is not as common as USG, sestamibi, and 4D-CT in current use, the results of studies with high-resolution magnetic resonance devices developed in parallel with technological developments are promising.[51]

Another method that has recently found wide coverage in the literature for parathyroid imaging is PET. With PET images taken using agents such as 18F-fluorocholine and 11C-methionine, parathyroid lesions can be detected at a rate of 93%-100%.[52] In the study of Amadou et al[53], in which the efficacy of fluorocholine PET and 4D-CT in reoperative parathyroidectomies was evaluated, it was reported that superior results were obtained with fluorocholine PET. In this study, in which 29 reoperative parathyroidectomy patients were examined, successful imaging was obtained in 63% of the patients and in 75% of the lesions with 4D-CT. On the other hand, successful imaging was performed in 85% of patients and in 96% of lesions with fluorocholine PET.[53] Positron emission tomography imaging with fluorocholine shows promising results, especially in reoperative parathyroidectomies.

In pHPT, localization can be detected in approximately 90% of primary cases with the above-mentioned imaging studies.[52] However, the success of localization studies also varies according to the center. There are reports that the sensitivity of preoperative imaging can be increased by up to 92% if patients with negative localization studies are re-examined in experienced centers.[54] In addition to these non-invasive examinations, invasive intervention methods such as bilateral jugular venous sampling, selective venous sampling, and parathyroid washout are also available. In addition to being invasive, the main handicap of these methods is that they require experience. In addition, there is a theoretical risk of parathyromatosis during parathyroid washout. Therefore, the use of invasive intervention methods is limited to reoperative cases that cannot be localized with classical imaging, mostly in high-volume centers.

Although preoperative imaging has no place in the diagnosis, there are reports that, after diagnosis, approximately 90% of endocrinologists have had at least one imaging method performed before referring patients to surgery.[55] Moreover, studies show that parathyroidectomy is delayed for an average of 2 years in patients with negative preoperative scintigraphy.[56] It is known that the probability of having MGD increases in patients with negative or discordant imaging.[47] However, it should not be forgotten that a single-gland adenoma still remains the primary cause in these cases. In addition, a negative localization study does not change the surgical indication. In these patients, a success rate of over 95% can be achieved with BNE.[57] Therefore, it would be a more appropriate approach to act in coordination with the surgeon who will perform the surgery when deciding which localization study to prefer. As a result, the success rate in preoperative imaging differs according to the type of examination preferred, the presence of MGD, and the experience of the interpreter. Preoperative imaging should be decided through a multidisciplinary approach of endocrinology, radiology, nuclear medicine, and surgery.

Surgical Treatment

The main goal in the surgical treatment of pHPT is the removal of diseased glands. Historically, because there was not as much knowledge on the pathophysiological basis of the disease as today, "bilateral neck exploration," in which all glands were explored and the glands that looked diseased were excised, was widely performed. But because 80%-85% of the disease comes from a single-gland adenoma and 80%-90% of the diseased glands can be located with imaging before surgery, people tend to choose less invasive surgical methods.[58] This evolutionary process in surgical preference has continued with the development of minimally invasive parathyroidectomy techniques called "unilateral neck exploration" and more recently focused/selective "parathyroidectomy." Currently, BNE or selective parathyroidectomy can be planned, depending on the etiology of the disease and the surgeon's experience. Although both approaches have satisfactory results in experienced hands, BNE is accepted as the gold standard approach in surgical treatment.[35] However, the popularity of selective parathyroidectomy techniques is increasing due to the development of the disease mostly on the basis of a single-gland adenoma and the developments in imaging methods.

The most important decision to be made in the management of pHPT is which surgical approach will be preferred. The main factor in determining the entry strategy is whether the patient has MGD. In this context, some variables can be used to help predict the presence of MGD in the preoperative period. The first variable is whether the disease has a genetic basis. Multiglandular disease is more likely in a pHPT developed on the background of MEN or familial isolated hyperparathyroidism. It is also known that the risk of MGD increases with lithium-associated pHPT. The biochemical variant of the disease can be used as the second variable. Studies show that the rate of MGD is <10% in hypercalcemic pHPT and >40% in normocalcemic pHPT.[59] In addition, in patients with a calcium value >12 mg/dL, the source of the pathology is almost always a single-gland adenoma.[59] As the third variable, the results of preoperative imaging methods can be used. In general, the pathological cause of pHPT is a single-gland adenoma in 80%-85% of cases, and MGD is responsible for approximately 10%-15% of cases. By accepting these rates as baseline values, the contributions of preoperative imaging methods can be evaluated. Accordingly, the probability of a single-gland adenoma is 90%-95% if sestamibi is positive and 60% if it is negative.[60,61] When the same evaluation is made for USG, the probability of a single-gland adenoma continues to be 85%, regardless of positive or negative imaging. In cases where 4D-CT is used for imaging, the probability of a single-gland adenoma is 95% in the presence of positive imaging and decreases to <60% in the case of negative imaging.[60,61] In this context, it can be said that USG does not change the conditional probability in the determination of MGD. If scintigraphy and 4D-CT support a single-gland adenoma, this situation makes a contribution to the conditional probability. Therefore, focused parathyroidectomy can be preferred as an entry strategy. However, if sestamibi and 4D-CT are negative, the most common cause is still a single-gland adenoma, but the possibility of MGD also increases. In such a case, it would be more appropriate to plan the initial strategy as BNE, or gradual parathyroidectomy, with intraoperative PTH monitoring.

Bilateral neck exploration requires exposure and evaluation of all parathyroid glands, including ectopic ones. Therefore, the surgeon is expected to have a good command of the parathyroid anatomy, to know where to look for glands, and to be capable of distinguishing between diseased and normal glands. The mainstay of the studies advocating BNE in surgical choice is based on the fact that there is no need for preoperative imaging and intraoperative adjunct techniques in the diagnosis of pHPT. Preoperative imaging and intraoperative adjunct techniques are integral parts of selective parathyroidectomy. These arguments are not needed in BNE. However, there are also studies showing that preoperative imaging studies increase treatment costs.[62] Aarum et al[62] evaluated the effect of preoperative imaging on the cost of treatment. In the study, the treatment costs and cure rates of the patients who underwent minimally invasive parathyroidectomy with sestamibi and USG and those who underwent BNE without localization studies were compared. The authors showed that high cure rates were obtained with no statistically significant difference in both surgical techniques, whereas localization studies increased treatment costs by 21%.[62] However, indirect factors that increase treatment costs, such as operation times, hospital stays, and readmissions due to surgical procedures, were not evaluated in the study. Udelsman[63] evaluated the results of 656 patients who underwent 401 BNE versus 255 patients with focused parathyroidectomy, considering these factors that indirectly increase treatment costs. In the study, local anesthesia was applied with cervical block in patients who underwent minimally invasive parathyroidectomy, and general anesthesia was used in patients who underwent BNE. Therefore, a reduction in anesthesia costs was achieved in the focused parathyroidectomy group. When indirect factors that increase the cost are included, it was concluded that the treatment costs for patients who underwent BNE almost doubled.[63]

There are many studies showing that selective parathyroidectomy has high cure rates, similar to BNE.[64-67] Moreover, in these studies, selective parathyroidectomy is generally associated with lower morbidity than BNE. However, the main limitation of studies in favor of selective parathyroidectomy is that their long-term results are not as clear as BNE. In addition, another striking point of the studies is that the rates of MGD were lower than the expected values. It should be noted that one of the most common causes of persistent or recurrent disease is MGD.[68] In this context, studies advocating BNE as an initial strategy suggest that the incidence of MGD is higher than that reported in selective parathyroidectomy studies. Therefore, it is emphasized that the glands that may cause recurrent disease in the future may be left in patients who underwent selective parathyroidectomy. For this purpose, Siperstein et al[69] investigated the presence of enlarged additional glands by continuing the dissection in patients with pHPT who underwent selective parathyroidectomy by preoperative USG + sestamibi. The study found that about one-fifth of patients who undergo routine BNE after selective parathyroidectomy have an additional enlarged gland. When selective parathyroidectomy is combined with intraoperative PTH monitoring, the rate of enlarged additional glands can be reduced from 20% to 16%. The authors stated that these additional enlarged glands, which they described as "pathological parathyroid glands of undetermined significance," may be the cause of recurrence in the future. Therefore, the argument that BNE is a more appropriate approach for the initial strategy of pHPT was highlighted in the study. Although an additional enlarged parathyroid gland was detected at a high rate of 20%, the pathological significance of these glands is not known. However, Mun et al[70] found no correlation between parathyroid gland size and excessive hormone production. From this point of view, even if an additional enlarged gland is left with selective parathyroidectomy, it is not expected to be a cause of recurrence. However, as mentioned before, the MGD rate in studies on selective parathyroidectomy is below the rates stated in the literature. This may be related to patient selection. However, Schneider et al[71] found no significant difference in recurrence between selective parathyroidectomy and BNE in 1000 patients in the long-term follow-up. Recurrence was not observed after the 36th month in the BNE group but continued in the selective parathyroidectomy group. This may be related to the enlarged additional glands left behind.

As a result, discussions continue in the literature about which initial strategy should be used. In general, the focus of the studies is based on cost analysis and success rates. There are many direct and indirect factors that affect the cost. Moreover, the impact value of each of these factors may differ according to the health systems and insurance coverages of the countries. Therefore, it can be accepted as an expected situation that different results will be obtained depending on which parameters are used in cost analysis and in which country the study is performed. However, in selected patients, selective parathyroidectomy provides high cure rates, similar to the results in BNE. Selective parathyroidectomy techniques have been the primary initial strategy for selected patients in experienced centers, although long-term outcomes are not as clear as BNE. However, it should be noted that while selective parathyroidectomy techniques are only an option for selected patient groups, BNE can be performed on all patients. In addition, BNE is indicated in patients who cannot achieve adequate PTH reduction with selective parathyroidectomy. Therefore, BNE can be performed both as a primary initial strategy and as a complementary surgery to selective parathyroidectomy. The fact that it can be performed on a wider spectrum of patients also makes BNE the gold standard. In light of these data, it can be said that instead of making comparisons over surgical techniques, detailed evaluation of the pathological basis of the disease and referral of patients to experienced centers for surgery are the most important factors in achieving success.

Intraoperative Adjunct Techniques

Parathyroid surgery has the potential to surprise the surgeon with every operation. Since the size of the parathyroid glands is not very large, it gives the feeling that not much is being done surgically. However, due to the anatomical and pathophysiological variations of the glands, it can be said that these operations are the most difficult operations of endocrine surgery. In this context, some intraoperative adjunct techniques have been developed to increase surgical success. Some of these techniques are used for "navigation" to help locate the pathological gland. Another area of use is to confirm that the excised gland is pathological, that is, "confirmation." Many intraoperative adjunct techniques have been described in the literature. Intraoperative parathormone monitoring (IOPTH-M), gamma probe, methylene blue, 5-aminolevulinic acid, nanocarbon, and indocyanine green angiography are examples of intraoperative adjunctive techniques.

Although many intraoperative adjunct techniques have been described, very few have found a place in routine use in clinical practice. Today, the most accepted adjunctive technique is intraoperative PTH monitoring. The half-life of PTH is 3-5 minutes. By using this feature, the adequacy of the dissection is confirmed according to the PTH levels measured before and after the excision of the pathological gland. Although many opinions have been reported about when PTH should be checked, the most accepted one is the Miami criteria.[38] In this context, it is considered sufficient if the PTH level measured at the tenth minute after the excision of the parathyroid gland, which is thought to be pathological, decreases by >50% compared to the highest basal PTH level measured before the incision or excision.[38] About 70%-90% of endocrine surgeons use IOPTH-M.[58,72] With the use of IOPTH-M, a trend has emerged in surgical preference from BNE to focal exploration.[58] Intraoperative PTH monitoring is one of the complementary arguments of selective parathyroidectomy techniques, just like preoperative imaging studies. While preoperative imaging determines where to start exploration, IOPTH-M determines where the dissection will be terminated. In patients whose preoperative USG and sestamibi scans show the same gland, the cure rate is 96.3% with selective parathyroidectomy without IOPTH-M. This rate can go up to 98.8% when IOPTH-M is used, though. In other words, the contribution of IOPTH-M is limited to patients with compatible imaging. However, in cases where only 1 of the USG and sestamibi are positive or both are positive but point to different glands, the contribution of IOPTH-M rises to 19%.[40]

By marking it with a USG before surgery, intraoperative navigational aids make it possible to see the parathyroid gland directly or indirectly during surgery. Nanocarbon, methylene blue, and gamma probes are the ones that have found use in these techniques. By injecting nanocarbon and methylene blue into the lesion, the parathyroid gland is made directly visible to the naked eye during surgery. In gamma probe technology, albumin labeled with Tc 99m is injected into the parathyroid gland under the guidance of preoperative USG. Unlike nanocarbon and methylene blue, the lesion is not seen as normal with the naked eye but can be detected indirectly with the gamma probe. The main handicap of these techniques is that they require invasive marking of the lesion in the preoperative period. Therefore, there is a theoretical risk of parathyromatosis albeit low. In addition, at least positive imaging should be obtained by USG. If it is to be performed only in USG-positive patients, it should be confirmed that the lesion is the parathyroid gland before the procedure, in which case it will be necessary to perform a PTH washout as a second procedure. In patients with positive USG as well as sestamibi in imaging, selective parathyroidectomy can already provide a high cure rate of 96.3% without intraoperative adjunct techniques.[73] Therefore, the contributions of these adjunct techniques are marginal. In light of these data, the use of these techniques is limited to reoperative cases, usually in tertiary centers.

The most popular adjunctive technique in recent years is indocyanine green angiography. Indocyanine green is a contrast agent that binds to plasma proteins and can be viewed with infrared cameras due to its fluorescent feature. It is not tissue or organ specific. However, target organs can be visualized by using infrared cameras since organs with a high blood supply, such as the parathyroid, emit more intense fluorescence. Due to this feature, the borders and viability of the organs can be evaluated relatively Indocyanine green angiography is used to both find the targeted parathyroid gland and evaluate the viability of the parathyroid glands after thyroidectomy. However, since it is not a tissue-specific agent, concomitant fluorescence of the thyroid gland is the most important handicap that limits its navigation feature.[74] Therefore, it is mostly used to evaluate the viability of the parathyroid glands to predict postoperative hypocalcemia after thyroidectomy. However, tissue damage may develop due to venous congestion or hematoma in the parathyroid glands during thyroidectomy. In such a case, the most important stimulus to raise awareness for the surgeon will be the color change in the parathyroid glands. However, this is a purely subjective criterion. In such cases, it is recommended to evacuate the hematoma by scratching the parathyroid capsule with the help of a needle or scalpel and to control the blood supply of the parathyroid gland. Indocyanine green angiography can be used as an alternative objective method to this subjective evaluation method. Ultimately, the main purpose of indocyanine green angiography is to evaluate the vascular structures and viability of the target organ.

Non-Surgical Minimally Invasive Treatment Methods

The role of medical and surgical approaches in the treatment of pHPT is well known. However, the search for alternative treatments to these classical methods continues. Imaging-assisted ablation of the parathyroid glands is the most widely used of these alternative treatment modalities. The ablation process provides necrosis in the target tissue by means of thermal or chemical agents, depending on the technique used. Thus, the ablated tissue becomes a target for the immune system and is destroyed. If heat-generating devices are used as the energy source, the process is called "thermal ablation." According to the energy source used in thermal ablation, it is classified as laser, radiofrequency, microwave, and high-intensity focused USG. The purpose of thermal ablation is to create coagulation necrosis by increasing the temperature locally in the tissue to a certain degree (although it varies according to the application time, irreversible tissue damage usually occurs between 40℃ and 600℃). The point to be noted here is that tissue damage at temperatures lower than 400°C is reversible. In addition, even if irreversible damage occurs in the ablated tissue due to evaporation and carbonization in the tissue at values above 1000°C, this tissue cannot be destroyed and has ceased to be a target for the immune system. If a chemical agent is used for ablation (usually ethanol), then the process is called "ethanol ablation." Ethanol causes coagulation necrosis by creating protein denaturation in the target cell, with the effect of dehydration. It also causes ischemic necrosis and vascular endothelial damage. Ablation procedures were initially used in thyroid cancer patients with metastatic lymph nodes who had serious surgical comorbidities. However, over time, it started to be used first in benign thyroid nodules and then in selected papillary microcancers. Although the success rates of the techniques vary according to the nodule structure and size, they are generally similar. However, the long-term consequences of ablation procedures for parathyroid adenomas are not as clear as for thyroid nodules. Moreover, the location of the parathyroid glands is in close proximity to the area formed by the trachea, esophagus, and recurrent laryngeal nerve, which is called the "danger zone" in ablation processes. Therefore, it is highly possible to develop complications with higher values than the expected complication rates due to an ablation procedure in thyroid nodules. Today, surgical treatment is the gold standard approach in the treatment of pHPT. However, ablation procedures may be a good alternative option in reoperational cases with serious comorbidities or in patients who do not want to accept surgery.

Conclusion

The incidence of pHPT is increasing in parallel with the development of health systems and screening programs. The diagnosis of the disease is entirely based on biochemical parameters. Imaging has no place in the diagnosis, and negative imaging tests do not affect the indication for surgery. The gold standard approach to treatment is surgery. Medical treatment is less effective and more costly than surgical treatment. There are options for surgical treatment, such as selective parathyroidectomy and BNE. The fact that the disease mostly originates from a single-gland adenoma and that the diseased gland can be localized in most of the patients with preoperative imaging methods has led to the widespread use of selective parathyroidectomy techniques. However, while selective parathyroidectomy is an option for selected patients, the fact that BNE is suitable for every patient makes BNE the gold standard approach in surgical treatment. The most important determining factor in surgical choice is the presence of MGD. Therefore, the histopathological basis of the disease should be well questioned. Although ablation methods have begun to take place in the treatment, the long-term results are uncertain.

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