ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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EFFECTS OF PREOPERATIVE FINDINGS ON POSTOPERATIVE RESULTS IN PATIENTS UNDERGOING SURGERY FOR PRIMARY HYPERPARATHYROIDISM

PRİMER HİPERPARATİROİDİ CERRAHİSİ GEÇİREN HASTALARDA PREOPERATİF VE PEROPERATİF PARAMETRELERİN KARŞILAŞTIRILMASI, PREOPERATİF PARAMETRELERİN POSTOPERATİF SEYRİ ÜZERİNE ETKİSİ

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Öz

Amaç
Çalışmamızda, primer hiperparatiroidi (p-HPT) nedeni ile opere edilen hastalarda görüntüleme yöntemlerinin başarısı ve preoperatif bulguların postoperatif sonuçlara etkisi araştırıldı.

Gereç ve Yöntem
Bu çalışmada Ocak 2008 ile Aralık 2010 tarihleri arasında Yüzüncü Yıl Üniversitesi Tıp Fakültesi Genel Cerrahi kliniği tarafından p-HPT nedeni ile opere edilen 50 ardışık olgunun verileri prospektif olarak incelendi. Çalışma süresi boyunca hastaların demografik verileri, klinik bulguları, ameliyat öncesi ve sonrası laboratuvar sonuçları, ameliyat öncesi dönemde lokalizasyon amacıyla yapılan ultrasonografi (USG), sintigrafi ve bilgisayarlı tomografi (BT) bulguları, ameliyat ve patoloji raporları incelendi ve kaydedildi. Elde edilen veriler istatistiksel olarak analiz edildi.

Bulgular
Kas iskelet sistemi ağrılarının en sık (%80) hastaneye başvuru nedeni olduğu görüldü. Opere edilen hastalarda ameliyat sonrası serum parathormon (PTH) ve kalsiyum seviyelerinin ameliyat öncesi döneme göre anlamlı oranda düştüğü tespit edildi ($p<0.05$). İki taraflı boyun diseksiyonu yapılan hastaların oranı %30 idi. Bezlerin histopatolojik incelemesinde hastaların % 88'inde adenom tespit edilirken paratiroid hiperplazisi olarak rapor edilenlerin oranı ise % 12 idi. Ayrıca hastaların % 4'ünde patolojik bezler ektopik yerleşimli (retroözofagial, ön mediasten) iken, % 4 hastada ise çift adenom mevcut idi. USG'nin patolojik bezleri tespit etmedeki sensitivitesi %72 olarak hesaplandı. Bununla birlikte USG'nin ektopik yerleşimli (%4) ve çift adenom (%4) olan lezyonların tamamında doğru lokalizasyon yapamadığı görüldü. Eş zamanlı tiroidektomi yapılan hastalarda, ameliyat sonrası kalsiyum değerleri tiroidektomi yapılmayanlara benzerken 2. gün PTH değeri daha düşük bulunmuştur.

Sonuç
Ultrasonografi yüksek tanısal değere sahip olmakla birlikte atipik yerleşimli, multipl lezyonlarda yanlış lokalizasyona sebep olabilmektedir. Cerrahi eksplorasyon arttıkça postop hipokalsemi riski artmaktadır.

Anahtar Kelimeler: Endokrin cerrahi, Paratiroid adenomu, Hiperparatiroidi.

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Abstract

Objective
To investigate the success of imaging methods and the effect of preoperative findings on postoperative results in patients who underwent surgery for primary hyperparathyroidism (p-HPT).

Material and Method
In this study, the data of 50 consecutive patients who underwent p-HPT surgery at the General Surgery Clinic of Yuzuncu Yil University Faculty of Medicine between January 2008 and December 2010 were prospectively analyzed. During the study period, the patients' demographic data, clinical findings, preoperative and postoperative laboratory results, findings of ultrasonography, scintigraphy, and computed tomography performed for localization in the preoperative period, and surgery and pathology reports were evaluated and recorded. The obtained data were statistically analyzed.

Results
Musculoskeletal pain was the most common (80%) reason for the patients' presentation to the hospital. In the operated patients, the serum parathormone and calcium levels significantly decreased compared to the preoperative period ($p<0.05$). The rate of patients who underwent bilateral neck dissection was 30%. In the histopathological examination of the glands, adenoma lesions were detected in 88% of the patients, and the rate of those with a pathology result of parathyroid hyperplasia was 12%. In addition, 4% of the patients had ectopic pathological glands (retroesophageal, anterior mediastinum), and 4% had double adenomas. The sensitivity of ultrasonography in detecting pathological glands was calculated as 72%. However, ultrasonography did not accurately localize all ectopic (4%) and double adenoma (4%) lesions. The postoperative calcium values were similar between the patients that underwent simultaneous thyroidectomy and those that did not undergo this operation, but the parathormone values measured on the second postoperative day were significantly lower in the former.

Conclusion
Although ultrasonography has a high diagnostic value, it can cause mislocalization in the presence of multiple lesions with atypical localization. The risk of postoperative hypocalcemia increases as surgical exploration increases.

Keywords: Endocrine surgery, Parathyroid adenoma, Hyperparathyroidism.

Introduction

Primary hyperparathyroidism (p-HPT) is a common endocrine disease that occurs as a result of the excessive and uncontrolled secretion of parathyroid hormone (PTH) from one or more glands. The main effects of PTH are calcium mobilization from bones and renal calcium reabsorption. The resulting hypercalcemia is the main biochemical manifestation of the disease. p-HPT can be seen throughout life but peaks in middle age. It is two to three times more common in women (1). The imaging of the parathyroid glands aims to determine the location of the glands before a surgical intervention rather than diagnosis. As localization methods, in addition to non-invasive options, such as ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), and sestamibi scintigraphy, there are invasive methods, including selective venous catheterization and angiography (2). In patients with recurrent HPT or a history of neck surgery, the necessity of a preoperative localization examination is indisputably accepted (3–5). In localization studies of parathyroid pathologies, the most commonly used imaging methods are USG and sestamibi scintigraphy. The sensitivity of the combined use of these two techniques has been reported to be between 70-90% (6-8).

This study aimed to investigate the success of imaging methods and the effect of preoperative findings on postoperative results in patients who underwent surgery for p-HPT.

Material and Method

This clinical study was prospectively conducted by examining 50 consecutive patients who underwent surgery with the diagnosis of p-HPT at the General Surgery Clinic of Yuzuncu Yil University Faculty of Medicine (YYUTF) between January 2008 and December 2010. The patients' demographic data, complaints, preoperative and postoperative laboratory findings, findings obtained from imaging examinations (USG, scintigraphy, and CT) performed to determine localization in the preoperative period, surgical findings, and histopathological examination results of

samples were recorded, and the obtained data were statistically analyzed.

The study was commenced after receiving approval from the ethics committee of YYUTF, dated 10.09.2008 and numbered 2008/08. Written informed consent was obtained from all participants. This study complies with universal ethical standards and the 1964 Declaration of Helsinki and its subsequent amendment. All the cases included in the study were patients who were evaluated by both the general surgery and endocrinology clinics and scheduled for surgery after the diagnosis of p-HPT was made. Patients diagnosed with secondary and tertiary HPT were excluded from the study. The diagnosis of p-HPT was diagnosed based on high serum calcium and parathormone levels, a low phosphate level, a high calcium level in spot urine, and normal kidney functions (9). Preoperative serum 25-OH vitamin D, thyroid-stimulating hormone (TSH), free T3 (fT3), free T4 (fT4), alkaline phosphatase (ALP), albumin, creatinine, creatinine in spot urine, calcium (Ca), and creatinine in 24-hour urine were also measured. The same endocrinology faculty member performed parathyroid adenoma localization in all the patients using preoperative USG. PTH values were determined in the serum samples obtained at the 30th minute after surgery (early PTH level), and in addition to PTH, calcium and phosphorus values were also measured in the serum samples taken on the postoperative first, second, and third days. The parathyroid gland was surgically removed, histopathologically examined in the pathology laboratory, and its weight and size were recorded.

Sestamibi scintigraphy was performed in 13 cases with indications. In addition, CT or MRI was performed in patients whose lesions could not be visualized with scintigraphy. The same surgical team with sufficient experience in thyroid and parathyroid surgery performed surgery in all the cases. The side of the lesion was explored in patients detected to have a single lesion on radiological images, and bilateral neck exploration in those with bilateral lesions or without any lesion detected by radiological imaging methods. In cases where p-HPT was accompanied by a thyroid nodule, lobectomy or bilateral total thyroidectomy was also performed.

Statistical Analysis

SPSS v. 17.0 software package was used for statistical analysis of the data. Categorical measurements (gender, complaint, comorbidity, surgical findings, and type of surgery) were obtained as numbers and percentages, and continuous measurements (calcium, phosphorous, urine calcium, PTH, alkaline phosphatase, and creatinine) as mean (and minimum-maximum where necessary). The independent-samples t-test was used to compare continuous measurements between the patient with and without hypocalcemia. The paired-samples t-test was conducted to compare time-varying dependent measurements, i.e., comparison of the values before and after surgery. The statistical significance level was taken as 0.05 in all the tests.

Results

Preoperative Characteristics

The preoperative characteristics of the patients are summarized in Table 1. Of the 50 patients included in the study, 84% were women. The mean ± standard deviation (SD) (minimum-maximum) value of age was 51.2 ± 11.23 (20-77) years. Ten patients were asymptomatic and diagnosed using the results of biochemical analysis. Among the common patient complaints at the time of presentation to the hospital were musculoskeletal pain (80%), gastrointestinal system complaints (burning sensation in stomach, etc.) (56%), and bone fractures (8%). Common comorbidities were thyroid nodules (56%), hypertension (24%), and nephrolithiasis (24%). Of the 25 cases in which bone mineral density was measured due to various indications, 11 had osteoporosis and 13 had osteopenia, and one had normal bone mineral density. In addition, two patients had a family member with multiple endocrine neoplasia (type 1 in one and type 2A in the other).

Preoperative Laboratory Values

The preoperative mean ± SD serum parathormone (488.94 ± 582.84 pg/ml), calcium (11.605 ± 1.56 mg/dL), and spot urine calcium (26.620 ± 18.06 mg/dL) levels were above the reference values. However, the mean ± SD serum phosphorus level was below the reference range (2.5072 ± 0.77 mg/dL). The urea and creatinine levels were normal in all the patients (Table 1).

Surgical Findings

Unilateral exploration was performed in 70% of the patients with a single adenoma detected by imaging methods. In 40% of these patients, lobectomy was added to treatment due to the presence of a thyroid nodule.

In 12% (n = 6) of the patients, the pathological parathyroid gland could not be removed at the first operation (persistent HPT). Unilateral exploration was performed in four of these patients. In the second operation

Table 1 Preoperative laboratory values of the patients

	n	Minimum	Maximum	Mean	SD
Age, years	50	20	77	51.22	11.235
Vitamin D (ref: 20-120 mg/L)	29	2.7	160.0	24.659	33.2288
Daily urine Ca (ref: 0-250 mg/dL)	45	77.0	450.0	218.49	8.7227
Daily urine Cr (ref: 11-20 mg/dL)	46	7.6	182.3	54.728	34.0673
Daily urine volume	46	460	2,200	1,146.09	408.142
Spot urine Ca (ref: 6.6-21.3 mg/dL)	48	2.5	94.5	26.620	18.0685
Spot urine Cr (ref: 0.7-1.5 mg/dL)	47	24.4	948.0	98.878	133.0383
Serum Cr (ref: 0.8-1.2 mg/dL)	50	0.3	1.2	0.671	0.2277
PTH (ref: 15-65 pg/ml)	50	94	2,900	488.94	582.844
Serum Ca (ref: 8.4-9.7 mg/dL)	50	10.0	19.2	11.605	1.5608
Serum P (ref: 2.7-4.5mg/dL)	47	1.00	5.10	2.5072	0.77236
ALP (ref: 5-270U/L)	50	106	3,068	507.90	583.083
Albumin (ref: 3.5-5.2 g/L)	50	3	5	4.36	0.412
24-hour urine Ca/Cr (0.09-0.16)	45	0.11	2.05	0.4927	0.31692
TSH (ref: 0.35-4.94 microU/l)	49	0.0	35.0	1.921	4.9696
fT3 (ref: 1.71-3.71pg/mL)	46	1.5	6.3	2.978	0.8069
fT4(ref: 0.7-1.8 ng/dL)	49	0.7	1.9	1.100	0.2691
Spot urine Ca/Kr (ref: 0.09-0.16)	47	0.03	2.06	0.3713	0.30914

ALP: Alkaline Phosphatase, Ca: Calcium, Cr: Creatinine, fT3: Free Tri-Iodothyronine (T3), fT4: Free Thyroxine (T4), P: Phosphorus, PTH: Parathyroid Hormone, SD: Standard Deviation, TSH: Thyroid-Stimulating Hormone

undertaken in these patients, adenoma lesions were found during bilateral exploration performed on average 4.6 days after the first operation.
In two patients who developed persistent HPT despite bilateral exploration, ectopic adenomas were removed during the reexploration procedure performed at 15 months and three months after the first operation, respectively.

Simultaneous with parathyroidectomy, bilateral total thyroidectomy (28%) was performed in 14 patients with thyroid nodules, thyroid lobectomy in the same number of patients [n = 9 (18%) on the right, n = 5 (10%) on the left], and total thyroidectomy on one side and subtotal thyroidectomy on the other side in one (2%) patient (Table 2).

Imaging and Localization Findings
In addition to neck USG performed in all the patients, sestamibi scintigraphy was undertaken in 13 cases, and localization examinations with CT and MRI in one patient. USG successfully detected the localization of pathological glands in 78% of the patients, this rate was 53.8% in scintigraphy.

Comparison of Preoperative Imaging and Surgical Findings
There was no relationship between the accuracy of localization with USG and adenoma size. The effect of USG on the diagnostic accuracy of pathological parathyroid gland localization was statistically significant ($p < 0.05$). It was determined that diagnostic accuracy was statistically significant in pathological parathyroid glands with a lower localization than those with an upper localization ($p < 0.001$). Pathological glands could not be accurately localized by USG in two patients with double adenomas. When the patients with and without consistent surgical findings and USG findings were compared, the mean preoperative PTH value was significantly higher in those with consistent findings ($p = 0.042$).

Table 2 Types of operations performed together with parathyroidectomy

	n	%
Only parathyroidectomy	21	42.0
Bilateral total thyroidectomy	14	28.0
Right lobectomy	9	18.0
Left lobectomy	5	10.0
Total thyroidectomy on one side and subtotal thyroidectomy on the other side	1	2.0
Total	50	100.0

Adenoma lesions were reported in 90.9% (n = 22) of the patients with serum vitamin D levels below 20 mcg/l. This rate was found to be 85.7% (n = 7) among the patients with a vitamin D level above 20 mcg/l.

Laboratory Findings

Table 3 presents the serum PTH levels of the patients at the postoperative 15th minute and the serum PTH, Ca, and P levels at the postoperative first, second, and third days. The mean serum PTH value significantly decreased in the early postoperative period compared to the preoperative period ($p < 0.05$). However, the serum PTH level significantly increased on the postoperative first, second, and third days compared to the early postoperative period ($p < 0.05$). This value exceeded the normal level in 22% of the patients on the postoperative third day (minimum: 67 pg/ml, maximum: 212 pg/ml).

When the serum calcium values were examined, there was a significant decrease on the postoperative first day compared to the preoperative value, but no significant change was found in the following days. In addition, postoperative manifest hypocalcemia (<7 mg/dl) developed in a total of six patients.

The serum phosphorus level significantly increased from the postoperative second day compared to the preoperative period ($p < 0.05$) (Table 4).

Pathology Findings

The histopathological diagnosis was in agreement with preoperative evaluation findings in 88% of the patients. However, in 12% of the patients, a frozen section examination was required in tissues considered to be parathyroid adenomas. Parathyroid adenomas were present in 44 patients who underwent surgery for p-HPT, and parathyroid hyperplasia was present in six patients. The smallest pathological parathyroid gland excised was 90 mg, and the largest gland was 11,600 mg. The mean gland weight was 1941,38 mg.

The histopathological characteristics of the cases that did and did not undergo simultaneous thyroidectomy (n = 29 and n = 21, respectively) are summarized in Table 5. In a patient who underwent bilateral total thyroidectomy and adenoma excision due to a multinodular goiter and parathyroid adenoma, the pathology result of the thyroid paraffin section examination was reported as papillary cancer. No additional surgical treatment was applied to this patient.

In the group that simultaneously underwent thyroidectomy, the PTH value was significantly lower on the postoperative second and third days ($p = 0.004$ and $p = 0.077$, respectively), and the phosphorus value was significantly lower on the postoperative first and second days ($p = 0.029$ and $p = 0.059$, respectively). When the postoperative serum calcium values were compared, no significant difference was found between the two groups ($p > 0.05$).

Discussion

Hypercalcemia is the main biochemical finding of p-HPT, which occurs as a result of the excessive and uncontrolled secretion of PTH from one or more glands. Although p-HPT can be seen at any age, and it is two to three time more common in middle-aged women (1). In the current study, the number of women with p-HPT was more than five times the number of men with this disease, and the mean age of all the cases was 51.2 years, which is consistent with the literature.

The clinical presentation of p-HPT has changed over the years, and the diagnosis of this disease is now

more frequently made based on biochemical/hormonal data alone in less symptomatic/asymptomatic patients. While nephrolithiasis was reported at a rate of 57% in earlier series, later studies indicated a much reduced rate, e.g., 17% reported (10). Twelve of our patients (24%) had a history of nephrolithiasis that could be directly associated with p-HPT. General complaints of the musculoskeletal system were present in 40% of the patients. To determine whether the complaints of patients with such non-specific complaints are associated with p-HPT, it is necessary to compare the incidence of these patient complaints with healthy individuals of similar age and characteristics in the medium-long term after surgery.

In light of the 2002 National Institutes of Health (NIH) conference surgical indication criteria, in the current study, three (6%) patients had urinary calcium excretion over 400 mg/day, 22 (44%) patients were aged below 50 years, 12 (24%) patients had a serum calcium value over 12 mg/dl, 29 (58%) patients had decrease of more than 30% in expected creatinine clearance according to age, and 12 (24%) patients had nephrolithiasis (11,12). When we evaluated five of the 2002 NIH operational criteria, namely age, history of urolithiasis, daily urinary calcium excretion, decrease in creatinine clearance, and serum calcium level, we determined that seven of the 50 patients did not meet any of these criteria, while two patients met four criteria. The mean number of criteria met by the patients was 1.56. It is possible that patients who underwent surgery without meeting the NIH criteria had other surgical indications that we did not evaluate in our study.

In this study, the mean calcium value was 11.6 mg/dl, and the calcium level was normal in two patients. In cases of vitamin D deficiency accompanying p-HPT, calcium can be found at normal levels.

The phosphorus level has been reported as 2.9 ± 0.1 mg/dl in cases with mild p-HPT (13). In our patient group, the mean phosphorus value was 2.5 mg/dl. Phosphorus deficiency was evident in 25% of the p-HPT cases. In addition, 30 patients (60%) had low phosphorus levels ($p < 2.7$). High phosphorus deficiency may be due to frequent vitamin D deficiency or the more severe course of p-HPT in our patient group. Although the vitamin D levels were lower in the patients with low phosphorus values, the difference was not statistically significant (17.9 ± 23.2 vs. 41.08 ± 46.8, $p = 0.089$).

The mean PTH level in mild p-HPT was previously reported as 121 ± 7 pg/ml (13). In our sample, the mean PTH level was 489 pg/ml, and the median PTH level was 276 pg/dl. This may be an indication that p-HPT was more severe in our patient group.

In patients with p-HPT, it is expected that the 25-OH vitamin D level is low, but the 1-25 OH vitamin D level is close to the upper limit (13). In our patient group, the mean 25-OH vitamin D level was 24.66 mcg/l. Among the 29 cases in which 25-OH vitamin D levels were measured, 10 had severe vitamin D deficiency (<10), and 12 had mild vitamin D deficiency (<30). Only seven patients had normal vitamin D levels. When the cut-off value of the vitamin D level was taken as 30 mcg/ml, it was determined that the mean calcium level was higher in the patients with a low vitamin D level compared to those with a normal vitamin D level. The phosphorus level of these patients being expected lower suggests that their high calcium level can be attributed to the more severe course of p-HPT only in these patients.

In mild p-HPT, the amount of urinary calcium excretion has been reported to be 248 ± 12 mg/day. Similarly, in our study, we found the amount of urinary calcium excretion as 218.5 mg/day. The moderate urinary calcium excretion level of our patients despite severe p-HPT may be related to their high concomitant vitamin D deficiency. It has been reported that urinary calcium excretion is lower and PTH levels are higher in p-HPT cases with low vitamin D levels (14). Although urinary calcium excretion was not correlated with the vitamin D level in our study, the amount of daily urinary calcium excretion was found to be lower in the patients with a low vitamin D level (177 mg/day vs. 277 mg/day, $p = 0.025$).

Parathyroid adenomas tend to be located more commonly in the lower pole (12). In the current study, parathyroid adenomas were found in the lower pole in most of the patients (58%). In some small adenomas, normal parathyroid tissue can be seen with a thin margin. The weight of the adenoma can vary from 300 mg to 6-7 g. Adenoma size ranges from 1 cm to 3-4 cm (15). In our patient group, the size of parathyroid adenomas ranged from 1 to 7.5 cm, and adenoma weight from 90 mg to 11.6 g. The mean adenoma weight was calculated as 1.9 g. These findings can be accepted as a further indication that p-HPT was more severe in our patients.

The sensitivity and specificity of sestamibi scintigraphy have been reported to be 50-100% and 75-100%, respectively (16). Concomitant thyroid pathologies can also have very important effects on scintigraphy findings. In our study, surgical findings were found

to be in agreement with scintigraphy findings in only seven (53.8%) of the 13 patients who underwent sestamibi scintigraphy.

In p-HPT, the sensitivity of USG in detecting the localization of enlarged glands is between 67 and 87% (17–21). Similar to the literature, in our study, the rate of agreement between USG and surgical findings was found to be 78%. We determined that the sensitivity of USG decreased in cases of atypical localization or double adenomas located in the upper pole.

Transient hypocalcemia is common after parathyroid surgery. Although transient hypocalcemia is seen in 10-20% of patients, this rate can increase to 35% in some series (22–24). The risk of transient hypocalcemia is low in mild HPT. If the parathyroids have been suppressed, secretion usually recovers rapidly within a few days. However, longer-term hypocalcemia may develop due to damage to the normal parathyroid glands or 'hungry bone syndrome'. Permanent hypoparathyroidism is seen in less than 1% of cases. In our study, there were 19 patients with a decreased phosphorus level on the postoperative third day compared to the preoperative value. In these patients, the vitamin D and urinary calcium excretion levels were higher compared to those with an increased phosphorus value, albeit not at a statistically significant level (26.9 vs. 12.2, p = 0.092 and 248.9 vs. 199.1, respectively; p = 0.083). These findings may indicate that higher vitamin D levels increase the risk of hungry bone syndrome development as a factor that accelerates mineralization.

The risk of permanent hypoparathyroidism after thyroid surgery varies depending on the extent of surgery. It may develop due to direct injury, unintentional removal, or devascularization of the parathyroids. In the current study, the serum calcium value decreased below 8.5 on the postoperative first day in 21 patients and remained below 8.5 mg/dl in 17 patients on the postoperative third day. On the postoperative third day, the PTH value increased in 35 patients compared to the earlier evaluation, and this decreased continued in 10 patients. The PTH value measured on the postoperative third day was below 10 in six patients. Since there was no long-term follow-up in our study, we do not know how many patients developed permanent hypoparathyroidism. However, we consider that these six patients are in the risk group. The common feature of this patient group is that all underwent bilateral exploration and thyroidectomy. Although the exact cause is unknown, increased bone turnover, increased ionized calcium levels, and suppression of parathyroid functions may play a role in hyperthyroidism.

It has been suggested that treatment of hyperthyroidism results in the increased mineralization of bone through a type of hungry bone syndrome. It has also been claimed that there may be overlooked damage in the parathyroids in some cases or calcium may decrease with the effect of calcitonin that enters circulation after thyroid manipulation (25). In our study, TSH was positively correlated with the postoperative third-day PTH and the increase in PTH from the early postoperative period to the postoperative third day. Similarly, the free T4 level was negatively correlated with the postoperative early PTH and postoperative third-day PTH levels. These findings may indicate that elevated thyroid hormone levels have a suppressive effect on postoperative PTH. The free T4 and post-operative second- and third-day calcium levels were found to be positively correlated. While elevated thyroid hormones increase calcium resorption from bones, they are also expected to decrease the PTH level. Our results suggest that high free T4 increased postoperative calcium and suppressed PTH for a longer time. Since the increase in TSH accompanies low thyroid hormone values, it is natural to see an increase in PTH. In a previous study, it was shown that the recovery of parathyroid cells was faster when surgical injury was applied to the parathyroid glands of rats in which hyperthyroidism was induced with TSH (26).

In p-HPT, tumor volume or weight is highly correlated with the serum calcium level. The mean correlation coefficient has been determined as 0.6, being reported to range from 0.4 to 0.8 (27-28-29). In our study, there was a significant correlation between adenoma weight and PTH and calcium levels (r = 0.633 and r = 0.47, respectively; p < 0.001 and p = 0.001, respectively). The correlation of calcium with PTH was similar (r = 0.46 p = 0.001). It is known that increased cell mass causes more PTH secretion and a higher calcium level. In our study, as adenoma weight increased, the postoperative early PTH value also increased (r = 0.804, p < 0.001). This may be due to the late clearance of high PTH or the introduction of more parathyroid hormone into circulation after the surgical manipulation of large parathyroid adenomas. The higher correlation between adenoma weight and the early PTH level compared to the baseline PTH strengthens the latter possibility. Adenoma weight was negatively correlated with the increase in PTH on the postoperative first and third days (r = 0.724, p < 0.001 and r = 0.338, p = 0.023, respectively). This is due to the inappropriate elevation of early PTH with surgical manipulation or greater suppression in the remaining parathyroids as the weight of the parathyroid gland increases. There was no significant correlation between the preoperative PTH value and the increase

in PTH on the postoperative third day compared to the earlier postoperative evaluation (p = 0.093). This suggests that the negative correlation of adenoma weight with the increase PTH on the postoperative first and third days was not due to the suppression of the remaining glands but related to the elevation in the early postoperative levels of PTH released from the gland through surgical manipulation. According to these findings, we consider that a relatively high early PTH value, especially after the removal of large lesions does not warrant doubting surgical success; rather, it indicates that the postoperative hypoparathyroidism risk of these patients should not be underestimated by examining early PTH levels.

In a previous study reporting the results of 51 patients who underwent surgery for p-HPT at our clinic between 1999 and 2002, nine (17.6%) patients had papillary thyroid cancer, nine had lymphocytic thyroiditis, two (3.9%) had benign thyroid adenomas, and 24 (47%) had nodular hyperplasia (30). In another study from Turkey evaluating 60 patients, thyroid cancer was detected in nine patients (15%), and thyroid pathologies were reported in a total of 40 patients (77%) (31). In another series including 194 patients who underwent minimally invasive parathyroid surgery, diagnosis was deemed suspicious on preoperative USG and biopsy, and thyroid cancer was detected in seven (5.5%) of the 23 patients who underwent thyroidectomy (32). In our study, thyroid cancer was detected in two of 29 patients (6.9% in the thyroidectomy group and 4% in the whole sample) who underwent thyroidectomy due to suspected thyroid pathologies during preoperative evaluation.

Conclusion

The PTH level and parathyroid weight of our patient group indicate moderate-severe HPT. Although vitamin D deficiency is common, it is not a risk factor for postoperative hypocalcemia. Although USG has a high diagnostic value, it may cause mislocalization in lesions with atypical localizations, those located in the upper glands, and multiple lesions. As surgical exploration increases, the risk of postoperative hypocalcemia also increases. This risk is even higher in patients that have undergone simultaneous thyroidectomy. The volume and weight of the parathyroid lesion are proportional to the degree of hypercalcemia and hyperparathyroidism. In p-HPT, an increase in calcium or a decrease in creatinine clearance may lead to a decrease in the renal phosphaturic effect of PTH.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study protocol was approved by Ethics Committee of Yuzuncu Yil University Faculty of Medicine (date-number: 10.09.2008-2008/08). All procedures performed in studies involving human participants comply with the universal ethical standards and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
İH: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

ÇK: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-review & editing.

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