

Retrospective Evaluation of Surgical Indications in Patients Presenting with Asymptomatic Primary Hyperparathyroidism: Single-Center Experience

Surgery Indications in Asymptomatic PTH Elevation

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ABSTRACT

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Objective: Primary hyperparathyroidism (PHPT) has evolved from a historically symptomatic disease to a predominantly asymptomatic condition, owing to advances in biochemical screening. This study delves into the retrospective evaluation of surgical indications and outcomes in asymptomatic PHPT patients, exploring the shift in disease presentation and the increasing incidence attributed to varied factors.

Materials and Methods: A review of asymptomatic PHPT cases diagnosed between January 2017-2022 was conducted at the Department of Endocrinology and Metabolism in İzmir Katip Celebi University, Atatürk Training and Research Hospital; surgical indications were assessed based on criteria outlined in the 4th International Workshop Asymptomatic PHPT guidelines.

Results: Among 48 patients (98% female, mean age 54.9 ± 5.9), 56.2% exhibited at least one surgical indication, with osteoporosis and renal complications being the most prevalent.

Conclusion: The study addresses the cautious approach to recommending parathyroidectomy in mild PHPT cases, emphasizing the criteria established by the 4th International Workshop. Contrary to the absence of long-term randomized research, recent meta-analyses and observational studies reveal limited changes in fracture rates, bone mineral density, nephrolithiasis, cardiovascular events, and quality of life. The debate over surgery benefits in non-surgical long-term follow-up remains to be conclusive. The study contributes valuable insights into the evolving landscape of surgical decision-making, emphasizing the need for further research on the long-term benefits and risks associated with surgery in this patient population. This retrospective analysis seeks to enhance our understanding of surgical interventions for asymptomatic PHPT and guide future clinical practices.

Asemptomatik Primer Hiperparatiroidili Hastaların Cerrahi Endikasyonlarının Retrospektif Olarak Değerlendirilmesi: Tek-Merkez Deneyimi

Asemptomatik PTH Yüksekliğinde Cerrahi Endikasyonları

Makale Bilgisi

ÖZET

Makale Geçmişi

Geliş Tarihi: 20/02/2024

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Anahtar Kelimeler:

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Paratiroid

Amaç: Primer hiperparatiroidizm (PHPT), biyokimyasal taramalardaki ilerlemeler sayesinde tarihsel olarak semptomatik bir hastalıktan ağırlıklı olarak asemptomatik bir duruma dönüşmüştür. Bu çalışma, asemptomatik PHPT hastalarında cerrahi endikasyonların ve sonuçların retrospektif değerlendirilmesini, hastalık prezantasyonundaki değişimi ve çeşitli faktörlere dayandırılan artan insidansı araştırmaktadır.

Gereç ve Yöntemler: Ocak 2017 ile Ocak 2022 arasında tanısı konulan asemptomatik PHPT olguları İzmir Katip Çelebi Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi Endokrinoloji ve Metabolizma Anabilim Dalı'nda detaylı olarak incelendi; olguların cerrahi endikasyonları 4. Uluslararası çalıştay asemptomatik primer hiperparatiroidizm kılavuzlarında belirtilen kriterlere göre değerlendirildi.

Bulgular: 48 hastanın (%98'i kadın, ortalama yaş 54,9 ± 5,9) %56,2'sinde en az bir cerrahi endikasyon mevcuttu; en yaygın olanları ise osteoporoz ve böbrek komplikasyonlarıydı.

Sonuç: Çalışma, 4. Uluslararası çalıştay tarafından belirlenen kriterleri vurgulayarak, hafif PHPT vakalarında paratiroidektomi önerme konusundaki ihtiyatlı yaklaşımı ele almaktadır. Uzun dönemli randomize araştırmaların bulunmamasına karşın, yeni meta-analizler ve gözlemsel çalışmalar fraktür oranlarında, kemik mineral yoğunluğunda, nefrolitiaziste, kardiyovasküler olaylarda ve yaşam kalitesinde sınırlı değişiklikler olduğunu ortaya koymaktadır. Cerrahi olmayan hastalarda uzun vadeli takipte cerrahinin faydaları konusundaki tartışma henüz kesinlik kazanmamıştır. Çalışmamız, cerrahi operasyona karar verme aşaması için değerli bilgiler katıyor ve bu hasta popülasyonunda cerrahinin uzun vadeli yararları ve riskleri hakkında daha fazla araştırma yapılması ihtiyacını vurguluyor. Bu retrospektif analiz, asemptomatik PHPT'ye yönelik cerrahi müdahalelere ilişkin anlayışımızı geliştirmeyi ve gelecekteki klinik uygulamalara rehberlik etmeyi amaçlamaktadır.

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Introduction

Primary hyperparathyroidism (PHPT) occurs from excessive parathyroid hormone (PTH) release from one or more parathyroid glands, making it a prevalent endocrine disorder. PHPT was generally recognized as a symptomatic disease with significant skeletal and renal complications between 1930 and 1970 (1). In recent years, asymptomatic hyperparathyroidism has increased because of the development of automated serum calcium measurement in the early 1970s and the determination of serum calcium levels in routine biochemical screening. A normocalcemic type of PHPT was discovered during the early 2000s (2). Epidemiological studies show that the annual incidence of hypercalcemia increases. The increasing occurrence of PHPT can be attributed to the phenomenon known as the "catch-up effect." However, several causes (such as environmental, dietary, or iatrogenic factors) that can lead to variations in PHPT incidence have been found (3,4). The diagnosis of asymptomatic PHPT is mainly based on the assessment of serum calcium and parathyroid hormone (PTH) levels, which can vary significantly across different countries and healthcare systems. The occurrence of PHPT is three to five times higher in postmenopausal women. Although the reason for this is not fully understood, it may be due to screening blood calcium and parathormone performed with the preliminary diagnosis of osteoporosis in postmenopausal women or routine calcium measurements (5).

Mostly, PHPT is due to a benign overgrowth of

one parathyroid gland (80% of cases) or a multiple gland disease (15–20% of cases) and rarely parathyroid carcinomas (<1%). Early diagnosis has resulted in a reduced occurrence of renal and skeletal diseases in addition to PHPT. In countries where biochemical screening is often conducted to diagnose osteoporosis or bone mass problems, the most prevalent manifestation of PHPT is the absence of symptoms. For the diagnosis of normocalcemic PHPT, secondary causes that increase PTH (vitamin D deficiency, renal insufficiency, malabsorption, medications such as lithium, biphosphonates, diuretics, and denosumab) must be excluded. The most common cause is vitamin D deficiency; PHPT may be underdiagnosed in areas where vitamin D deficiency is common (4,6).

General symptoms are due to target organ dysfunctions (bone cysts, Brown tumors, renal Stones and impairment, peptic ulcers, pancreatitis, proximal muscle weakness) (4). There are various opinions about which PHPT with only biochemical abnormalities should be operated on. Parathyroidectomy is the most proven approach for patients having symptomatic primary hyperparathyroidism (nephrolithiasis, pathological fractures, symptomatic hypercalcemia) (7).

However, there have also been reports of fatigue, anxiety, decreased ability to concentrate, cognitive decline, and worse quality of life, but they are not specific to PHPT. Asymptomatic PHPT is defined in

patients with definite primary hyperparathyroidism by laboratory tests and without clear signs of target organ manifestations. Asymptomatic PHPT can progress into symptomatic disease in one-third of the individuals during the follow-up (8). In asymptomatic PHPT, the DEXA measurement of bone, especially cortical bone, suggests osteopenia. Studies showed that not only cortical but also trabecular bone was affected, which explains the increased fracture risk (9). In a PHPT, bone involvement is usually obscure, and DEXA measurement and other bone imaging techniques may show the extent of the disease (10).

The most common clinical manifestation of primary hyperparathyroidism (PHPT) is asymptomatic PHPT detected by routine biochemical screening. In asymptomatic patients, PHPT may be clinically silent for years or may progress by creating a surgical indication.

This single-center observational, descriptive retrospective study aimed to evaluate the indications for surgery in patients with asymptomatic PHPT.

Materials and Methods

We examined the surgical criteria of patients diagnosed with asymptomatic PHPT at the Department of Endocrinology and Metabolism in Izmir Katip Celebi University School of Medicine, Ataturk Training and Research Hospital, from January 2017 to January 2022, using the hospital's information processing

system. The study was approved by the Ethics Committee of Izmir Katip Celebi University Faculty of Medicine (2022/0567).

Asymptomatic patients with PHPT were defined as patients without clinical signs and symptoms specific to elevated PTH and/or hypercalcemia. Inclusion criteria in the study: 1. Osteoporosis (T-score <-2.5 at lumbar, spine, total hip, femoral neck, or distal 1/3 radius with DXA), 2. Renal complications (creatinine clearance <60 mL/min, 24-hour urine calcium >400 mg/day, and presence of nephrolithiasis or nephrocalcinosis with ultrasound or CT scan), 3. Age <50 , 4. Serum calcium >1.0 mg/dL above the upper reference limit.

It was evaluated with four main criteria in accordance with the 4th International Workshop Asymptomatic Primary Hyperparathyroidism guidelines. Study exclusion criteria: 1. Patients with normocalcemic hyperparathyroidism, 2. Asymptomatic hyperparathyroidism patients who are recommended surgery without evaluating renal and bone complications, 3. Patients with symptomatic hyperparathyroidism. Demographic and laboratory data were also evaluated. SPSS version 22.0 software (Armonk, NY: IBM Corp) was used for statistical analysis. Results are reported as mean \pm SD for continuous variables, percentage for categorical variables, and median (IQR) for numerical variables.

Results

Forty-eight patients were included in this study. 47 (98%) patients were female and 1 (2%) was male, with a mean age of 54.9 ± 5.9 (42-67). The mean calcium, phosphorus, vitamin D, and PTH levels were 11.3 ± 0.4 mg/dl, 3.0 ± 0.4 mg/dl, 26 ± 7 μ g/L, and 111 ± 35 ng/L, respectively. The mean parathyroid volumes of patients who underwent parathyroidectomy were measured as 0.78 ± 0.24 cc. Surgically localized parathyroid adenomas of operated patients were in the right lobe in 59% and the left lobe in 41%. The demographic and clinical characteristics of patients with asymptomatic hyperparathyroidism are shown in Table 1.

In this study, 27 (56.2%) patients had one or more surgical indication criteria. None of the patients had all surgical criteria categories. The most common surgical indication association was renal and bone complications in 7 (15%) patients. The proportions of other surgical indications are given in Table 2.

Discussion

Clinicians have been cautious in recommending parathyroidectomy in mild PHPT with moderate hypercalcemia and no known morbidities due to the absence of long-term randomized research. Most clinicians follow the criteria of the 4th International Workshop Asymptomatic Primary Hyperparathyroidism guideline published in 2014 until 2022 (10). This study was completed before 2022.

A recent meta-analysis of randomized clinical trials and observational studies in patients with asymptomatic and uncomplicated PHPT found no significant changes in bone fractures, BMD changes, nephrolithiasis, cardiovascular events, or even quality of life, neuropsychiatric symptoms comparing the efficacy of parathyroidectomy and active surveillance (11). There is an inadequate amount of observational data about patients with asymptomatic PHPT who have not undergone surgery, and some adverse effects can be observed in long-term observations. However, the complications of the operation should be evaluated in addition to the disease. The long-term data are needed to understand who benefits from surgery in the long term. Patients with normocalcemic hyperparathyroidism have more skeletal progression than typical in PHPT, according to Lowe and colleagues' study. However, the investigation was carried out exclusively on patients who underwent screening for osteoporosis, and this may affect the result (12). In other studies, fracture and cardiovascular diseases do not increase, and there is no progression to hypercalcemia (13,14). Although short-term follow-up and a minor patient group were performed, no significant disease progression was observed in the studies (13,14). Moreover, according to the guidelines, there is no evidence of progression in patients with normocalcemic PHPT (15). It is still controversial which patients will progress in non-surgical long-term follow-up and whether the predictions are sufficient. Most patients are diagnosed during osteoporosis screenings, and patients who are followed up without surgery may have

osteoporosis progression. During a 15-year follow-up study, 25% of non-surgical asymptomatic PHPT patients showed disease progression at 10 years and 37% at 15 years. It is essential to regularly monitor these patients who initially do not fit the surgical criteria (8). Fifteen years after the PHPT surgery, improvements were seen in the bone's cortical and cancellous regions, mainly in the cancellous region (16). Studies of mortality associated with asymptomatic PHPT are minimal. In one study, 19% of patients in the non-surgery group died during the 15-year follow-up, and most deaths were cardiovascular disease-related (8). However, other studies indicate that overall survival is not affected, but patients with severe PHPT have an increased mortality risk (17). In the most extended prospective clinical study to date, Pretorius et al., a total of 101 patients' morbidity events (cardiovascular events, cerebrovascular events, cancer, peripheral fractures, and kidney stones) were similar between groups. Moreover, 18% of the patients followed in their study, which extended to the second 10 years and gave the results, were transferred to the surgery group due to high calcium. Parathyroidectomy does not appear to reduce morbidity or mortality in mild PHPT. This study also showed no evidence of adverse effects of observation for at least ten years in terms of fractures, cancer, cardiovascular and cerebrovascular events, or renal morbidities (18). Yeh et al. In their first systematic evaluation, in which they investigated compliance with the consensus guidelines for the surgical treatment of PHPT, 20% of the patients with asymptomatic hyperparathyroidism had an elevated calcium

level, 16% had 24-hour urinary calcium >400 mg/dl, and 17% were < 50 years old. They found it to be smaller than 6% and have the low bone density for age in 6% of them as surgical criteria. An additional surgical indication was found in 39% of the patients with Ca>11.5%. The same study found surgical criteria in 51% of asymptomatic patients (19). Within our analysis, osteoporosis and renal problems emerged as the prevalent surgical indications, with 27 patients (56.2%) meeting at least one requirement for surgical intervention.

In a prospective research involving 122 patients, it was shown that there was a notable rise in BMD after parathyroidectomy in the individuals who underwent surgery. In contrast, 21% of the patients who did not undergo surgery experienced a notable decline in their BMD during the 10-year follow-up period (7). In our study, following these data, osteoporosis was the most critical operation indication in asymptomatic patients.

In one study, 52 patients with PHPT who were asymptomatic and had similar baseline tests were followed for ten years, and progression was seen in 27% of the patients. 2 of the patients had hypercalcemia (serum calcium concentration of more than 12 mg per deciliter), 8 had hypercalciuria (urinary calcium excretion of more than 400 mg per day), and 6 had low cortical bone density (Z score for the distal third of the radius, less than -2), and none of them had fractures or

nephrolithiasis (20).

Conclusion

No study has been reported explicitly examining the indications for surgery in asymptomatic patients in our country in the literature. The clinical presentation of PHPT may differ according to vitamin D and geographical regions. In this single-center descriptive study, bone and renal complications were the most frequent indications for surgical criteria in asymptomatic PHPT patients.

Limitations

This study has potential limitations. Firstly, it was a retrospective study; therefore, there are no long-term observations. Moreover, the sample size is small and as this is a single-centered study. It can be corrected with a bigger sample size and multi-center study.

Ethics Approval: In compliance with the Declaration of Helsinki, our Institutional Non-Interventional Clinical Research Ethics Committee approved the study (Approval no:0567, 22/12/2022). Informed Consent: It is a retrospective study, so there isn't needed.

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Table 1. Demographic and clinical characteristics of patients with asymptomatic hyperparathyroidism

Characteristics	Mean value (n:48)
Age (year)	54.9 ± 5.9(42-67)
Sex	
Male	1 (%2)
Female	47 (%98)
Parathyroid adenoma volume (cc)*	0.78 ± 0.24
Baseline level of serum Calcium (mg/dL)	11.3 ± 0.4
Baseline level of serum Phosphorus (mg/dL)	3.0±0.4
Baseline level of serum ALP (u/L)	87.21 ± 21.56
Baseline level of serum PTH (ng/L)	111±35
Vitamin D level (µg/L)	26 ± 7
Location of parathyroid adenoma*	
Left lobe inferior	9 (%41)
Right lobe inferior	16 (%59)

PTH: Parathyroid hormone; ALP: Alkaline phosphatase; *:Only underwent parathyroidectomy.

Table 2. Rates of surgical criteria in patients with asymptomatic hyperparathyroidism

Osteoporosis	%31
Renal Complications	%21
Renal and Bone Complications	%15
Age<50	%13
Calcium level>11.5 mg/dl	%10