

# Correlation of intraoperative parathyroid hormone levels of primary hyperparathyroidism with single adenoma volume and weight: Can optimal criteria be created to end the surgery?

## Primer hiperparatiroidizmde intraoperatif paratiroid hormon düzeylerinin tek adenom hacmi ve ağırlığı ile ilişkisi: Cerrahi sonlandırmak için optimal kriterler oluşturulabilir mi?

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### SUMMARY

**Objective:** To study the relationship of intraoperative parathormone (PTH) decrease levels with solitary parathyroid adenoma (SPA) weight, diameter, and volume of the adenoma in patients with primary hyperparathyroidism (PHPT).

**Method:** Prospectively evaluation of consecutive patients undergoing parathyroidectomy (PTx) with the diagnosis of PHPT related to SPA. Perioperative biochemical parameters of patients; volume, weight and diameters of adenoma were recorded. Intraoperative PTH drop percentages were calculated. Adenoma diameter and volume were measured and calculated using preoperativ ultrasound. Adenoma was weighed intraoperatively by the surgeon.

**Results:** Forty-five consecutive patients underwent PTx for a SPA between October 2018 and October 2019. There were 9 men and 36 women, with a mean age of  $51 \pm 14.94$  years. A positive correlation was identified between the volume with the weight and maximum diameter of resected parathyroid glands ( $r = 0.613$ ,  $p < 0.001$ ;  $r = 0.871$ ,  $p < 0.001$ , respectively). There was a positive correlation between volume and preoperative PTH levels, albeit a weak one ( $r = 0.334$ ,  $p = 0.025$ ). No significant relationship was found between adenoma volume and ioPTH drop rate ( $r = 0.088$ ,  $p = 0.565$ ).

**Conclusions:** We have not been able to establish criteria based on correlation between PA volume and weight and the ioPTH drop rate that would allow us to make decisions on ending the parathyroidectomy and reducing persistent PHPT cases.

**Keywords:** Solitary parathyroid adenoma, intraoperative parathyroid hormone, parathyroid gland volume, parathyroid gland weight.

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## ÖZET

**Amaç:** Primer hiperparatiroidizm (PHPT) hastalarında intraoperatif parathormon (PTH) azalma düzeylerinin soliter paratiroid adenom (SPA) ağırlığı, çapı ve adenom hacmi ile ilişkisini incelemek.

**Yöntem:** SPA ile ilişkili PHPT tanısı ile paratiroidektomi (PTx) geçiren ardışık hastaların prospektif olarak değerlendirilmesi. Hastaların perioperatif biyokimyasal parametreleri; adenomun hacmi, ağırlığı ve çapları kaydedildi. İntraoperatif PTH düşüş yüzdeleri hesaplandı. Adenom çapı ve hacmi preoperatif ultrason kullanılarak ölçüldü ve hesaplandı. Ameliyat sırasında cerrah tarafından adenom tartıldı.

**Bulgular:** Ekim 2018 ile Ekim 2019 arasında 45 ardışık hastaya SPA için PTx uygulandı. Yaş ortalaması  $51 \pm 14.94$  olan 9 erkek ve 36 kadın vardı. Rezeke edilen paratiroid bezlerinin ağırlığı ile hacim ve maksimum çapı arasında pozitif korelasyon belirlendi (sırasıyla  $r=0.613$ ,  $p<0.001$ ;  $r=0.871$ ,  $p<0.001$ ). Hacim ile ameliyat öncesi PTH düzeyleri arasında zayıf da olsa pozitif korelasyon vardı ( $r=0,344$ ,  $p=0,025$ ). Adenom hacmi ile ioPTH düşüş oranı arasında anlamlı bir ilişki bulunamadı ( $r=0.088$ ,  $p=0.565$ ).

**Sonuç:** Paratiroid adenom hacmi ve ağırlığı ile ioPTH düşüş oranı arasındaki korelasyona dayalı, paratiroidektomiye sonlandırma ve persistan PHPT vakalarını azaltma konusunda karar vermemize izin verecek kriterleri belirleyemedik.

**Anahtar sözcükler:** Soliter paratiroid adenomu, intraoperatif paratiroid hormonu, paratiroid bezi hacmi, paratiroid bezi ağırlığı.

## INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disease with curative treatment parathyroidectomy (PTx), which is caused by solitary parathyroid adenoma (SPA) and has a prevalence rate of 80%–85%<sup>1,2</sup>. For SPA-related PHPT cases, whether there is a significant relationship between the weight, diameter, and volume of the adenoma and the biochemical parameters of hyperparathyroidism and the rate of intraoperative parathormone (PTH) decrease remains controversial<sup>3-7</sup>. With the possibility of a correlation between these parameters, the question of whether the criteria for adequate and curative surgery differs in weight and diameter in SPAs becomes relevant. If this correlation is revealed, it may be possible for surgeons to decrease the rate of persistent or recurrent hyperparathyroidism. Due to the lower success rate and higher mortality and morbidity of reoperations for persistent or recurrent primary hyperparathyroidism, detection and excision of all enlarged parathyroid tissue in the first surgery is the main purpose of operative management in PHPT<sup>8</sup>.

In our literature review (PubMed), a prospective study investigating the relationship between the biochemical parameters of hyperparathyroidism and SPA volume measured by ultrasound (USG) and the adenoma weight measured intraoperatively in the preoperative period was not identified. Our aim in this study was to investigate the relationship between SPA volume measured by USG in the preoperative period and intraoperatively measured adenoma weight and ioPTH drop rates as criteria to decide to end the surgery.

## MATERIAL AND METHODS

This study was conducted prospectively with the approval of our institution's ethics committee. Patients who underwent PTx with the diagnosis of PHPT related to SPA in Ondokuz Mayıs University Faculty of Medicine General Surgery Department were included in this study. A single general surgeon conducted resected parathyroid adenoma in all these patients (C.P.).

Among the patients who applied to our clinic, patients with hypercalcemia (calcium > 10.6 mg/dl) and high plasma intact PTH (> 65 pg / mL), 24-h urinary calcium levels > 100 mg/dL, as well as patients who had pathological confirmation of parathyroid adenoma or parathyroid hyperplasia were included in the study. Patients with multiple endocrine neoplasia, multiple gland disease, and parathyroid cancers as well as patients who were operated for secondary and tertiary hyperparathyroidism were excluded.

The age and gender of the patients were recorded. Serum calcium, phosphorus, PTH, creatinine, albumin, alkaline phosphatase (ALP), and serum 25 (OH) D (ng/mL) levels were studied preoperatively, postoperative 24 h, postoperative 3 months, and postoperative 6 months. In addition, PTH was studied at the tenth minute intraoperatively. Parathormone drop percentage (% decrease in ioPTH) was calculated according to the differences between preoperative PTH and intraop 10-min PTH.

All patients underwent preoperative localization investigations using a high-resolution neck USG and Tc99m-sestamibi scintigraphy. USG examinations of the patients were performed by a

radiologist and a surgeon using a Siemens ACUSON S2000 (Siemens Medical Solutions, MountainView, CA, USA) equipped with an 18-MHz transducer. All patients were positioned supinely, with the neck slightly extended. During B-mode examination, the size of the lesion in three diameters and its volume were noted. The volume calculation was based on ellipsoid assumption in which the volume was calculated as length x breadth x height x 0.523. The localizations (upper right, lower right, upper left, lower left, and intrathyroidic) of SPAs detected by preoperative USG were recorded. Intraoperatively, cases in which the SPA detected in localization was incompatible with that determined in USG were excluded from the study.

The indications for PTx include symptomatic PHPT, and asymptomatic PHPT with one or more criteria (patient's serum calcium level, bone mineral density, the risk of a fragility fracture, kidney stone, or a reduction in creatinine clearance), as defined by the National Institute of Health guidelines<sup>9</sup>.

A planned focused PTx was performed on all patients. Four patients had partial thymectomy, and one with papillary thyroid cancer had PTx and total thyroidectomy. The resected parathyroid gland was weighed and recorded in grams intraoperatively by the surgeon. Although a 50% reduction in postexcision PTH has been described as a criterion for successful exploration, we preferred to also observe a postexcision level that fell within the normal range. Frozen sections were made in all cases. After applying study inclusion criteria, the study population was composed of 45 PHP patients who underwent PTx with a minimum of 6 months postoperative follow-up. Patients with serum PTH, calcium, and phosphorus results within normal limits at the postoperative sixth month were also considered as having sufficient surgery and curative treatment.

Correlation coefficients were calculated for parathyroid adenoma weight and volume with preoperative biochemical markers. The percentage decrease of PTH levels from baseline 10 min postexcision were also correlated with parathyroid adenoma weight and volume.

## Statistical Analysis

All statistical analyses were performed using IBM SPSS V23. Compatibility with normal distribution was checked with the Shapiro Wilk test. The relationship between the volume values without normal distribution and other parameters was evaluated with Spearman rank correlation. The significance level was taken as  $p < 0.05$ .

## RESULTS

Forty-five consecutive patients with PHPT were included in our research, and they underwent PTx. Nine (20%) of the patients were man, 36 (80%) were women, and the mean age was  $51 \pm 14.94$ . Localization of adenomas was found in the lower right at 14 patients (31%), lower left at 12 patients (27%), upper right at 10 patients (22%), and upper left at 9 patients (20%). In 1 (2%) case, papillary thyroid cancer also accompanied parathyroid adenoma. Four (9%) of the adenomas were located intrathyroidically (Table 1).

As shown in Table 2, the mean preoperative parathyroid hormone level was  $161.52 \pm 133.73$  pg/mL, mean serum calcium was  $10.91 \pm 0.50$  mg/dl, and mean serum phosphorus was  $2.77 \pm 0.46$  mg/dl. The weight of adenomas ranged between 0.19 to 6.04 g, with a mean weight of  $1.40 \pm 1.20$  g. Adenoma volume ranged from 0.05 to  $8.05 \text{ cm}^3$ , with a mean volume of  $1.08 \pm 1.47 \text{ cm}^3$  measured by USG. The mean maximal diameter of adenomas was  $18.38 \pm 9.19$  mm. The mean percentage decrease of intraoperative postexcision PTH levels was  $72.20 \pm 16.02$  at 10 min.

As shown in Table 3, a positive correlation was identified between the volume with the weight and maximum diameter of resected parathyroid glands ( $r=0.613$ ,  $p < 0.001$ ;  $r=0.871$ ,  $p < 0.001$ , respectively). There was a positive correlation between volume and preoperative PTH levels, albeit a weak one ( $r=0.334$ ,  $p=0.025$ ). Furthermore, a negative and weak significant correlation between volume and preoperative serum phosphorus ( $r= - 0.309$ ,  $p=0.039$ ) was identified. No significant relationship was found between adenoma volume and ioPTH drop rate ( $r=0.088$ ,  $p=0.565$ ).

**Table 1:** Study patient population characteristics (N = 45)

Patient Characteristics	Number of Patients (%)
Gender	
Man	9(20)
Women	36(80)
Age (years), mean± s.d.	51±14.94
Location	
Right inferior parathyroid gland	14(31)
Right superior parathyroid gland	10(22)
Left inferior parathyroid gland	12(27)
Left superior parathyroid gland	9(20)
Intrathymic	
Yes	4(9)
No	41(91)

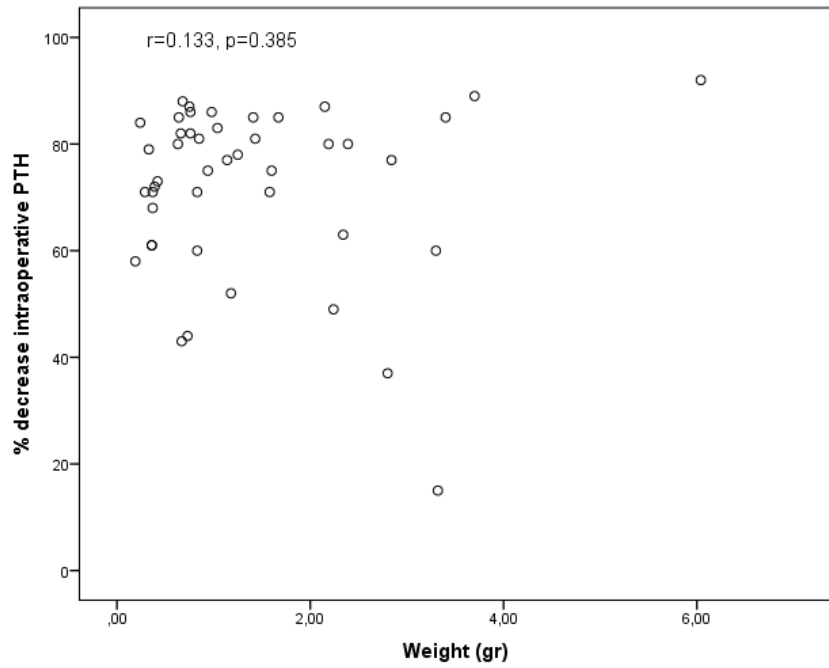
**Table 2:** Baseline laboratory parameters in the study subjects (N = 44)

Parameter	Mean	Median(Range)
Preoperative Serum		
PTH (pg/mL)	161.52 ± 133.73	132.60(41.65-904.9)
Alkaline phosphatase (U/L)	131.47 ± 162.91	96.50(51-1070)
Calcium (mg/dL)	10.91 ± 0.50	10.90(9.6-11.8)
Phosphorus (mg/dL)	2.77 ± 0.46	2.82(1.82-3.64)
Creatinine (mg/dL)	0.72 ± 0.17	0.71(0.39-1.07)
25-OH-D levels (ng/ml)	13.55 ± 8.04	10.85(2.37-32.46)
IoPTH(pg/mL)	42.02 ± 54.31	29.64(13.08-382.60)
(%)decrease in ioPTH	72.20 ± 16.02	77.00(15.00-92.00)
Postoperative 1st day		
Serum PTH(pg/mL)	24.40 ± 14.04	22.00(5.27-63.74)
Serum Calcium (mg/dL)	8.86 ± 0.55	8.90(7.90-10.50)
Postoperative 6 <sup>th</sup> month		
Serum PTH (pg/mL)	68.70 ± 34.37	62.00(20.00-205.60)
Serum Calcium (mg/dL)	9.52 ± 0.45	9.53(8.60-10.40)
Adenoma characteristics		
Weight(gr)	1.40 ± 1.20	0.94(0.19-6.04)
Volume (cm <sup>3</sup> )	1.08 ± 1.47	0.44(0.05-8.05)
Maximal Diameter (mm)	18.38 ± 9.19	16.20(6.90-45.50)

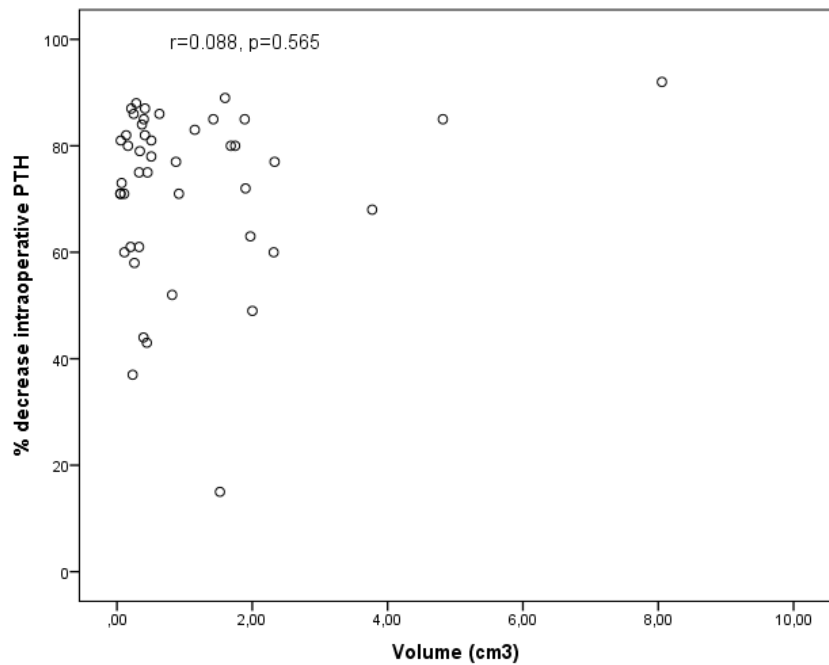
**Table 3:** Examining the relationship between the volume of adenoma (cm<sup>3</sup>) and parameters

	r	p
Age	0.218	0.149
Preoperative Serum		
PTH	0.334	<b>0.025</b>
Calcium	0.199	0.189
Phosphorus	-0.309	<b>0.039</b>
Alkaline phosphatase	0.186	0.263
25-OH-D levels	-0.215	0.177
ioPTH	0.235	0.121
% decrease in ioPTH	0.088	0.565
Weight	0.613	<b>&lt;0.001</b>
MaximalDiameter	0.871	<b>&lt;0.001</b>

r: Spearman correlation coefficient



**Figure 1:** Relationship between parathyroid adenoma weight (gr) and percentage decrease of intraoperative PTH levels at 10-min postexcision.



**Figure 2:** Relationship between parathyroid adenoma volume (cm<sup>3</sup>) and percentage decrease of intraoperative PTH levels at 10-min postexcision

There was no significant relationship between weight and decrease in ioPTH ( $r = 0.133$ ,  $p = 0.385$ , Figure 1). Similarly, there was no significant relationship between volume and decrease in ioPTH ( $r = 0.088$ ,  $p = 0.565$ , Figure 2)

## DISCUSSION

Many algorithms and criteria have been proposed to determine the success of PTx, including the most accepted Miami criterion<sup>10,11</sup>. However, none of them have managed to minimize persistent HPT rates. The effect of ioPTH reduction rate on appropriate surgery decisions and the many factors affecting this rate have been discussed<sup>11-16</sup>. In our opinion, if the success rates of PTx can be increased by using an algorithm or certain criteria, it would be possible to reduce both reoperations and complications. The relationship between parathyroid adenoma diameter, volume, and weight and preoperative biochemical parameters remains controversial<sup>1-7,17</sup>. These two pieces of information raise the following questions: Is there a relationship between SPA volume and weight and ioPTH drop rate for SPA? If any, in order to terminate the operation in all SPA cases, can an algorithm or certain criteria be created by measuring adenoma volume and/or by considering the weight of intraop adenoma with preop USG instead of 50% ioPTH drop rate? Can the number of persistent or recurrent HPT be reduced? Can we manage to reduce morbidity by reducing secondary surgeries?

In many studies examining the relationship between adenoma volume and weight and biochemical parameters, such as PTH, calcium, and phosphorus, the information in pathology reports for adenoma volume and weight was used retrospectively and was calculated according to the dimensions in the volume pathology reports<sup>1,4,6,7,12</sup>. In our study, unlike other studies, adenoma volume and dimensions were measured by USG in the preoperative period, and the weight was taken by the surgeon when the specimen was removed intraoperatively. According to our results, there is a correlation between adenoma volume and weight and largest diameter values ( $r=0.613$ ,  $p<0.001$ ;  $r=0.871$ ,  $p<0.001$ , respectively). Whereas there was a weak correlation between volume and preop PTH ( $r = 0.334$ ,  $p = 0.025$ ), no correlation was found with serum calcium ( $r=0.199$ ,  $p=0.189$ ). A negative correlation was found between volume and phosphorus ( $r = - 0.309$ ,  $p = 0.039$ ). Moretz et al., in common with us, reported a correlation between volume and PTH, but no correlation between volume and calcium<sup>7</sup>. Kamani et al., also in common with Moretz et al., reported in a

prospective study involving 69 patient, a correlation between volume and PTH and calcium ( $r = 0.327$ ,  $p = 0.006$ ;  $r = 0.333$ ,  $p = 0.005$ , respectively), but the phosphorus value was not correlated with weight and volume ( $r = -0.101$ ,  $p = 0.410$ ;  $r = -0.188$ ,  $p = 0.122$ , respectively)[3]. Randhawa et al. reported that there was no relationship between adenoma and biochemical markers in a retrospective study involving 77 consecutive PHPT patients<sup>17</sup>. We believe that there is a correlation between adenoma volume and weight and the biochemical parameters of hyperparathyroidism as reported in many studies in the literature<sup>1-7</sup>.

In our literature review (PubMed), we found only a few articles investigating the relationship between ioPTH drop rate and adenoma volume and weight<sup>7,18,19</sup>. Most of the articles sought answers to questions, such as how many minutes should ioPTH be run after excision, what the PTH drop rate should be, or how to calculate the drop rate based on the preop highest PTH value or PTH viewed before starting surgery<sup>11-16</sup>. Ours was the first prospective study to investigate the relationship between ioPTH drop rate and adenoma volume and weight in PHPT cases.

There are three studies investigating the relationship between ioPTH drop rate and SPA volume and weight. These studies were conducted by Moretz et al., Fang et al. and Ahmadi et al.<sup>7,18,19</sup>. Fang et al.<sup>18</sup> and Ahmadi et al.<sup>19</sup> carried out their investigations in patients with secondary hyperparathyroidism. The only study of PHPT cases that is similar to ours, albeit retrospectively, was the study of Moretz et al.<sup>7</sup>. In our study, there was no correlation between ioPTH drop rate and weight and volume ( $r = 0.133$ ,  $p = 0.385$ , Figure 1;  $r = 0.088$ ,  $p = 0.565$ , Figure 2, respectively). Fang et al.<sup>18</sup> claimed that there was a correlation between weight and volume and reduction of PTH, although they implemented their studies using SHPT cases. Ahmadi et al.<sup>19</sup> reported that there was no relationship between adenoma mass, and PTH. Moretz et al.<sup>7</sup> indicated that the ioPTH drop rate was correlated with weight but did not find any correlation with volume, as in our study. Our study did not support the results of Moretz et al. and other studies. According to our results, although there was a correlation between adenoma volume and preop PTH, we could not use this as a criterion in terminating the operation, because there was no relationship between PA volume and weight and ioPTH drop rate.

The strengths of our study included the fact that the surgery was performed by a single operator, and

potentially confounding double adenomas, multi gland hyperplasia, renal hyperparathyroidism, and parathyroid carcinoma cases were excluded. This is the only study in which parathyroid adenoma weight was measured intraoperatively by the surgeon for analysis and in which volume and diameter were measured directly with preoperative USG.

### Limitations

In terms of limitations, the authors agree that conducting this study with 45 patients included the likelihood of potential confounding factors.

Researchers and medical practitioners have not yet been able to create an algorithm or criteria that allows decision on terminating the operation by considering PA volume and weight and the ioPTH decrease rate in order to reduce persistent PHPT cases. However, studies on the relationship between ioPTH drop rate and adenoma volume and weight should continue with prospective randomized studies performed within a longer timeframe and with more cases.

### CONCLUSION

At this time, we have not been able to establish criteria based on correlation between PA volume and weight and the ioPTH drop rate that would allow us to make decisions on ending the parathyroidectomy and reducing persistent PHPT cases.

**Ethics Committee Approval:** The study protocol was approved by the Ondokuz Mayıs University Faculty of Medicine Institutional Ethics Committee (approval no: 2018/272, date: 25.06.2018).

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