

Pre-operative Parathormone Levels are Correlated with Mean Diameter of Parathyroid Adenoma and Pre-operative Serum Calcium and Alkaline Phosphatase Levels

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Abstract

The aim of the present study was to determine the relationship between biochemical parameters, mean diameter of parathyroid adenoma (MDPA) and parathyroid hormone (PTH) levels in patients who underwent parathyroid surgery. **Materials and Methods:** Data were collected retrospectively from patients with hyperparathyroidism who were operated and followed in our hospital between September 2011 and April 2014. Twenty-nine (male/female = 8/21) patients with a mean age of 58.31 ± 12.59 years were enrolled into the study. The mean pre-operative serum calcium and intact PTH (iPTH) levels were 11.98 ± 1.23 mg/dl and 386.52 ± 374.96 pg/ml, respectively. Serum pre-operative calcium levels were found to be significantly higher in patients who had nephrolithiasis than those who did not, whereas pre-operative serum phosphate levels were lower. Pre-operative iPTH levels were found to be correlated with pre-operative calcium, alkaline phosphatase and MDP, but not with pre-operative serum phosphate. Also, pre-operative calcium levels were found to be significantly correlated with MDP. **Conclusion:** Presence of nephrolithiasis is associated with higher pre-operative calcium and lower phosphate levels. Pre-operative iPTH and calcium levels were also found to be significantly correlated with MDP; this suggests that serum iPTH and calcium levels can be useful in predicting MDP.

Keywords: Hypercalcemia, primary hyperparathyroidism, parathyroid adenoma, parathormone, calcium

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Introduction

The parathyroid glands regulate calcium homeostasis in the human body by parathormone (PTH) secretion. The primary role of the PTH is to maintain serum calcium levels in the normal range. Hyperparathyroidism is caused by overproduction of parathyroid hormone. Primary hyperparathyroidism (PHPT) is the most common cause of hyperparathyroidism which occurs in a setting of excessive PTH secretion with an autonomous parathyroid gland, resulting in hypercalcemia [1]. High levels of PTH cause serum calcium levels to increase and serum phosphate levels to fall. A noncancerous growth (adenoma) on a gland is the most common cause of PHPT. Hyperplasia of two or more parathyroid glands accounts for most other cases. Most patients with PHPT have a single adenoma (about 80% of cases). Multigland disease can occur in 10%–15% of cases and double adenomas in 4%-5% [2]. Parathyroid carcinoma is seen in less than 1% of PHPT patients [3,4]. PHPT usually occurs randomly, but some people inherit a gene that causes the disorder [5].

Secondary hyperparathyroidism (SHPT) is characterized by high PTH and low serum calcium levels. PTH is elevated due to decreased levels of calcium or 1,25-dihydroxyvitamin D₃. Chronic renal failure is the most common cause of SHPT. Failing kidneys do not convert enough vitamin D to its active form, and they do not adequately excrete phosphate. This leads to hypocalcemia and a subsequent increase in PTH secretion in an attempt to increase the serum calcium levels. Other less common causes of SHPT are long-term lithium therapy, vitamin D deficiency, gastrointestinal malabsorption syndromes (when the intestines do not absorb vitamins and minerals properly), malnutrition, vitamin D-resistant rickets, or hypermagnesemia [6].

Tertiary hyperparathyroidism (THPT) occurs after in patients with long-term SHPT. Parathyroid glands become autonomous, producing excessive PTH even after the cause of hypocalcemia has been corrected and this results in hypercalcemia. Long-term kidney disease is the most common cause of THPT [1].

Assessment of serum calcium, phosphate and PTH levels together with neck ultrasonography, computerized tomography (CT) scanning, magnetic resonance imaging (MRI) and dual-phase (99m)Tc-sestamibi (methoxyisobutylisonitrile [MIBI]) imaging aid in the diagnosis of parathyroid lesions.

Parathyroid surgery to remove the overactive tissue (adenoma, or adenomas) is the only definitive treatment for PHPT, particularly if the patient has a very high serum calcium level or has had a bone fracture or a kidney stone. In asymptomatic patients, guidelines are used to identify who might benefit from parathyroid surgery [7,8]. During the “standard parathyroid operation”, the surgeon identifies all four parathyroid glands and removes whichever one(s) is enlarged. The vast majority of time there is just one large parathyroid gland (an adenoma which is a benign parathyroid tumor) and three normal parathyroid glands. In this situation the parathyroid adenoma would be removed leaving the three normal parathyroid glands to function in a normal fashion indefinitely. If the surgeon found all four parathyroid glands to be enlarged (found in only 2-3% of patients and called "parathyroid hyperplasia"), he/she would typically take out 3 or 3 1/2 of these glands (subtotal parathyroidectomy) leaving some parathyroid tissue behind to function normally in the future. In experienced hands this surgery has a cure rate of about 95 percent [9]. Subtotal and total parathyroidectomy with autograft are the two widely-accepted surgical procedures for treating THPT [10,11].

In light of this background knowledge, we conducted a retrospective study in patients who underwent parathyroid surgery in our hospital. The aim of the present study was to determine the relationship between biochemical parameters, mean diameter of parathyroid adenoma (MDPA) and PTH levels in surgically treated patients.

Materials and Methods

Medical records of patients with hyperparathyroidism who had been operated and followed in our hospital between September 2011 and April 2014 were collected retrospectively. Twenty nine (8 males, 21 females) patients were identified through our hospital's database and enrolled in the study. Pre-operative blood urea nitrogen (BUN), serum creatinine, calcium, phosphate, alkaline phosphatase (ALP), albumin, intact PTH, 25-hydroxyvitamin D (25-OHD), serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH); and postoperative calcium, phosphate and iPTH levels were obtained from all patients. Pre-operative imaging methods including parathyroid ultrasonography, Tc99m MIBI, CT, MRI of the neck, and positron emission tomography (PET) scan were also recorded.

Inclusion criteria were an elevated PTH level in addition to high serum calcium and low/or near-normal serum phosphate levels (all calcium levels were corrected based on albumin

levels). Exclusion criteria included the presence of overt hyperthyroidism, malignancy and/or use of any drug which could affect serum calcium levels. Based on the aforementioned inclusion criteria, PHPT was considered in 28 patients and THPT in one patient with chronic kidney disease who was on haemodialysis treatment. This patient also had the highest iPTH level (Table-1).

Since this was a retrospective study, none of the patients had 24-hour urinary calcium excretion tests. Results of bone mineral density testing and conventional bone radiographic images were also absent. In our medical database, not all diameters of the parathyroid adenomas were recorded; thus, parathyroid adenoma volume could not be measured. Therefore, the “mean diameter of parathyroid adenoma” (MDPA) was estimated using arithmetic mean of the diameters. MDPa was also included to our data.

None of the patients had been given vitamin D3 replacement therapy before the parathyroid surgery.

Statistical analysis

All statistical analyses were done using the Statistical Package for Social Sciences (SPSS for Windows, version 15; Chicago; IL). Since the data were distributed homogenously, statistical analysis was done with parametric tests. The results were presented as mean, standard deviation (SD), median, minimum and maximum. Comparisons between two groups of data were evaluated using the independent samples t-test. Relationship between continuous variables was tested by Pearson's correlation coefficient (r) analysis. Statistical significance was set at a p-value less than 0.05.

Results

Twenty-nine (8 males and 21 females) patients with mean age of 58.31 ± 12.59 years (range, 31-84) were included in the study. The mean age was 53.88 ± 14.89 years (range, 31-78) for the males and 60.00 ± 11.55 years (range, 37-84) for the females.

There was not a difference between males and females with respect to age. Pre- and post-operative laboratory tests of the patients are summarized in Table-1.

Table 1. Results of pre- and post-operative laboratory tests of the study patients

Parameter	Mean (SD)	Median (min-max)	Reference range	Unit
Pre-op BUN	26.31±17.48	20 (6.00-77.00)	20.00-40.00	mg/dl
Pre-op creatinine	0.92±0.39	0.80 (0.50-2.34)	0.70-1.40	mg/dl
Pre-op calcium	11.98±1.23	11.80 (10.60-15.90)	8.70-10.20	mg/dl
Pre-op phosphate	2.48±0.65	2.30 (1.70-4.60)	2.40-5.10	mg/L
Pre-op 25-OHD	14.34±9.18	11.00 (4.00-32.00)	15-65	ng/ml
Pre-op albumin	4.19±0.55	4.30 (2.50-5.00)	3.20-4.80	g/dl
Pre-op ALP	141.41 ±62.63	123.50 (71.00-322.00)	45.00-129.00	U/L
Pre-op iPTH	386.52±374.96	232.00 (83.00-1454.00)	25.00-80.00	pg/ml
MDPA	16.15±6.00	15.00 (5.00-35.00)	--	mm
Post-op calcium	9.34±0.77	9.40 (7.6-11)	8.70-10.20	mg/dl
Post-op phosphate	3.35±0.97	3.45 (1.50-5.40)	2.40-5.10	mg/dl
Post-op iPTH	27.69±35.00	15 (3.00-168.00)	25.00-80.00	pg/ml

SD: Standard deviation, min: minimum, max: maximum, pre-op: pre-operative, post-op: post-operative, BUN: Blood urea nitrogen, 25-OHD: 25-hydroxyvitamin D, ALP: alkaline phosphatase, PTH: parathormone, MDPA: Mean diameter of parathyroid adenoma.

Hypercalcemia was due to primary hyperparathyroidism (PHPT) in 28 patients and due to CRF-related THPT in 1 patient. Five patients had a history of nephrolithiasis due to PHPT, whereas 21 patients did not. Significantly higher serum pre-operative calcium levels and lower serum phosphate levels were found in patients who had nephrolithiasis than those who did not. Although MDPA seemed to be greater in patients with nephrolithiasis compared to those without nephrolithiasis, there was not a statistically significant difference between 2 groups (Table-2).

Table 2. Pre-operative laboratory tests of the patients with or without nephrolithiasis

Nephrolithiasis		Present (n=5)	Not present (n=21)	p
Pre-op Ca (mg/dl)	Mean (±SD)	13.02±1.96	11.76±0.95	0.006
	Median (min,max)	12.00 (11.50-15.90)	11.75 (10.06-13.90)	
Pre-op P (mg/dl)	Mean (±SD)	2.12±0.15	2.55±0.70	0.017
	Median (min,max)	2.10 (1.90-2.30)	2.30 (1.70-4.60)	
Pre-op iPTH (pg/ml)	Mean (±SD)	573±506	347±342	0.386
	Median (min,max)	315(234-1430)	208 (83-1454)	
MDPA (mm)	Mean (±SD)	25±10	15±4.55	0.116
	Median (min,max)	25 (15-35)	15 (5-25)	

SD: Standard deviation, Min: Minimum, Max: Maximum. Pre-op: Pre-operative, Ca: Serum calcium level, P: Serum phosphate level, iPTH: Serum intact parathormone level, MDPA: Mean diameter of parathyroid adenoma.

Pre-operative 25-OHD tests were available in only 17 patients out of 29 and 4 of them had a result equal to or greater than 20 ng/ml. Pre-operative laboratory results were not found to be different in patients with pre-operative 25-OHD levels $\geq$ 20 ng/ml compared to those with levels below 20 ng/ml (data not shown).

Pre-operative iPTH levels were found to be correlated with pre-operative calcium, ALP and the mean diameter of the parathyroid adenoma [(r=0.468, p=0.011; r=0.714, p<0.001 and r=0.531, p= 0.005, respectively) [Figures 1, 2, 3]. Additionally, pre-operative calcium levels were significantly correlated with MDPA [(r=0.576, p=0.002), Figure 4].

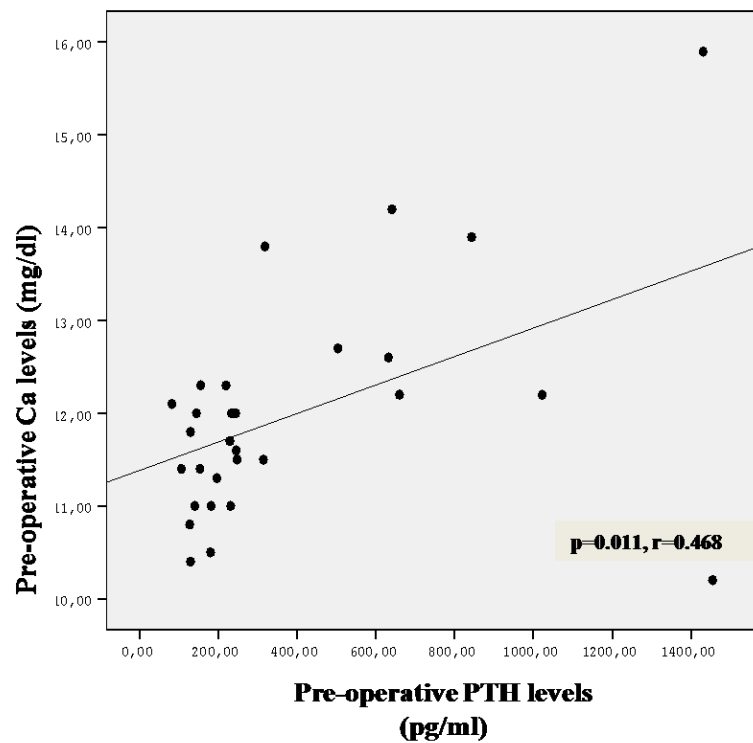


Figure 1. Correlation between pre-operative Ca and PTH levels

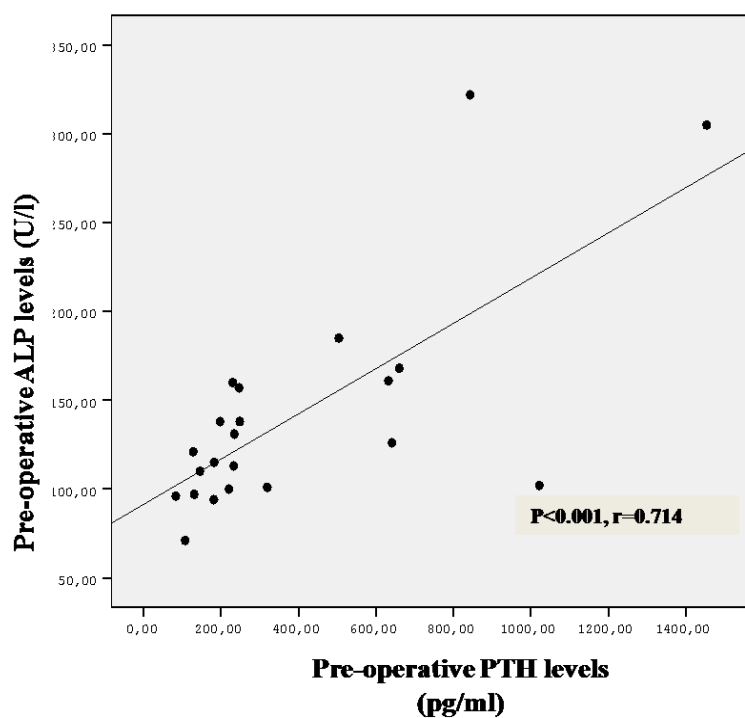


Figure 2. Correlation between pre-operative ALP and PTH levels

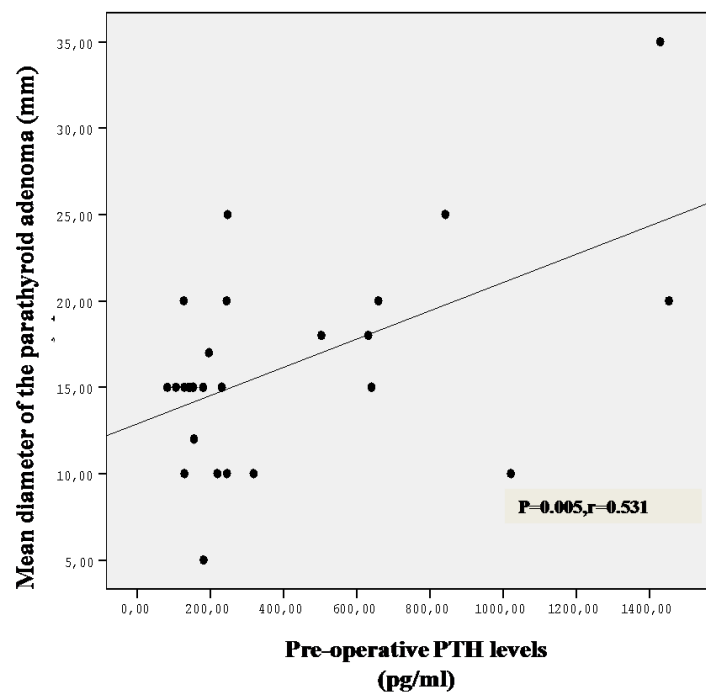


Figure 3: Correlation between mean diameter of the parathyroid adenoma and pre-operative PTH levels

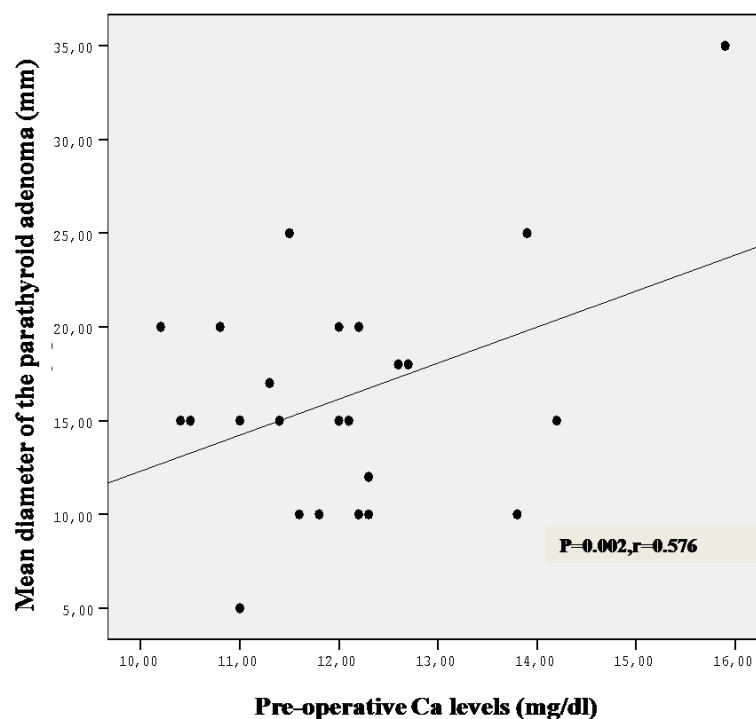


Figure 4. Correlation between mean diameter of the parathyroid adenoma and pre-operative Ca levels

All patients underwent ultrasound examination and dual-phase ^{99m}Tc-sestamibi (Tc^{99m} MIBI) parathyroid scintigraphy imaging. During the ultrasound examination and Tc^{99m} MIBI imaging, 23 and 24 parathyroid adenomas were detected respectively. MRI and conventional CT of the neck were performed for 2 patients each, and PET imaging for 1 patient because of negative ultrasound imaging. Only in one patient, parathyroid adenoma was detected by conventional neck CT and Tc^{99m} MIBI. A visible parathyroid adenoma could not be demonstrated by imaging only in 4 patients. After the operation, calcium and iPTH levels returned to normal in all patients except one. This patient was a 45 year-old male who had an unsuccessful parathyroid surgery with pre-operative serum calcium and iPTH levels of 11 mg/dl and 182 pg/ml, respectively. His pre-operative 25-OHD test was not available. Neither ultrasonography, nor Tc^{99m} MIBI could detect a parathyroid adenoma. Following parathyroid surgery, a parathyroid adenoma was detected by pathological examination of the specimen. Therefore, serum calcium and iPTH levels were not found to be decreased after the surgery.

After the parathyroid surgery, none of the patients experienced “hungry bone syndrome”, therefore, there was no need for calcium replacement. All parathyroid specimens were examined histopathologically. All of the identified adenomas were solitary and benign and none of them were diagnosed as “parathyroid carcinoma”. All patients were referred to an outpatient general surgery clinic for routine follow-up after the parathyroidectomy operation.

Discussion

PHPT accounts for about 90% of hypercalcemia cases in ambulatory patients, and 20% to 30% of hypercalcemia cases in hospitalized patients. Although this condition may occur at any age, it commonly affects general population over the age of 50 years and postmenopausal women [12]. Complete surgical resection of a hyperfunctioning parathyroid adenoma (or tissue) is essential for the treatment of PHPT (or THPT), particularly in patients presenting with symptoms related to the effects of PTH on the bone and kidneys [1, 2, 5, 9]. Available surgical options range from a minimally invasive parathyroidectomy to a bilateral neck exploration. Regardless of the surgical approach, the likelihood of success is highest with an experienced endocrine surgeon at a reference center [10, 11].

In the present study, 28 patients underwent parathyroid surgery because of PHPT and one patient for THPT due to severe hypercalcemia. Serum pre-operative calcium levels were found to be higher in patients who had nephrolithiasis than those who did not. This is reasonable because higher serum calcium levels are associated with higher urinary calcium levels which can lead to nephrolithiasis. As shown in our study, higher serum calcium and lower phosphate levels result in an elevation of PTH levels. Thus, higher serum calcium levels can be related to MDPa. In our study, MDPAs were found to be statistically non-significantly greater in patients with nephrolithiasis.

Hypercalciuria is one of the several factors associated with formation of renal calculi. A 24-hour urinary calcium, adjusted for the GFR, may aid diagnosis if familial hypocalciuric hypercalcemia is part of the differential diagnosis. In our study, all patients were operated because of severe hypercalcemia; so, there was no need for an exploration of the patients for hypercalciuria. If a pre-operative consultation with an endocrinologist had been done, it could have been helpful in the differential diagnosis of familial hypocalciuric hypercalcemia.

The diagnosis of PHPT mainly depends on laboratory findings and parathyroid imaging has no role in the diagnosis of PHPT. Imaging findings only have a role in guiding the surgeon to determine the site of the adenoma. In the present study, 29 patients underwent parathyroid surgery and 25 of them had a visible single adenoma as detected by imaging methods pre-operatively. After the parathyroid surgery, 28 patients were cured except 1. In this patient, a decrease in serum calcium and iPTH levels was not observed after the surgery despite performing a 2-gland parathyroidectomy. In the same patient, parathyroid adenoma could not be detected by pre-operative imaging either. Thus, unsuccessful surgery might have been predictable for this case. If endocrinology consultation had been performed pre-operatively for this patient, subtotal parathyroidectomy (3 1/2 gland resection) could have been planned before the surgery. Effective collaboration between different specialties including internal medicine (particularly endocrinology), radiology, nuclear medicine, and surgery may increase the surgical success rates. We would like to underline the importance of consultations between the surgeons and these specialties before deciding on a parathyroidectomy operation.

In the current study, calcium, phosphate, ALP, 25-OHD and iPTH, the parameters of bone metabolism, were investigated. IPTH levels were found to be correlated with serum ALP

levels. Since high ALP activity suggests increased bone turnover, it was not surprising to observe a correlation between iPTH and ALP levels.

Vitamin D deficiency occurs more frequently in patients with PHPT compared with the general population, and is usually associated with an aggravated form of the disease. In our retrospective study, we observed that most of the patients had vitamin D insufficiency and none of them had been given replacement therapy. Current guidelines recommend measurement of serum levels of 25-OHD in all patients with PHPT, and their repletion if the levels are less than 50 nmol/l (20 ng/ml) [13]. Limited data suggest that vitamin D treatment is generally safe in individuals with mild PHPT and coexisting vitamin D deficiency. Adverse effects include hypercalcuria and, less commonly, exacerbation of hypercalcemia [14]. Well-designed trials are needed to evaluate the safety of vitamin D3 replacement therapy in a wide spectrum of patients with concomitant PHPT and vitamin D deficiency. These trials should address the impact of such therapy on the complications and course of PHPT.

In the present study, pre-operative iPTH levels were found to be correlated with MDP and serum calcium and ALP levels. Pre-operative calcium levels were also correlated with MDP. There are some studies that investigated the relationship between parathyroid adenoma volume (and weight) and serum calcium and PTH levels [15, 16]. In a retrospective study including 30 patients (8 men, 22 women), a significant correlation was identified between pre-operative serum calcium and parathyroid adenoma weight. A significant correlation was also shown between baseline iPTH measurements and parathyroid adenoma volume. Thus, the authors concluded that pre-operative serum calcium and baseline iPTH levels may be useful in predicting parathyroid adenoma weight and volume, respectively [15]. On the other hand, in a separate study, pre-operative iPTH levels were found to be correlated with parathyroid adenoma volume, but not with serum calcium levels [16]. In another retrospective study which reviewed medical records of 63 patients with solitary adenomas, pre-operative serum calcium and PTH levels were found to be associated with parathyroid adenoma volume and weight, but not with serum phosphate levels [17].

In a prospective study, while there was a positive correlation between pre-operative serum calcium, PTH, ALP and adenoma weight, pre-operative serum phosphate was not correlated with adenoma weight [18].

In the present study, pre-operative iPTH and calcium levels were found to be significantly correlated with MDPa but not with pre-operative phosphate levels. Thus, we believe that pre-operative iPTH and calcium levels can be useful in predicting MDPa and vice-versa.

In conclusion, presence of nephrolithiasis was found to be associated with elevated pre-operative calcium and lower phosphate levels. Pre-operative iPTH and calcium levels showed a significant correlation with MDPa, suggesting that serum iPTH and calcium levels may be useful in predicting MDPa.

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