ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Paratiroid Adenomlu Hastaların Analizi: 6 Yıllık Tek Merkez Deneyimi

Analysis of Parathyroid Adenoma Patients: A Single Center 6 Year Experience

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ÖZ

Giriş: Primer hiperparatiroidizm yaygın bir kalsiyum metabolizması bozukluğudur. Primer hiperparatiroidizmi olan hastalar iskelet ve böbrek hasarı açısından risk altındadır. Primer hiperparatiroidizm ile D vitamini eksikliği birlikteliği kesin tanı koymada güçlüklere yol açabilir. Merkezimizde paratiroid adenomu hastalarının klinik özelliklerini ve laboratuvar bulgularını gözden geçirdik ve hastaların D vitamini durumundan bağımsız olarak paratiroid adenomu tanısı için olası bir yönlendirici parametre bulmaya çalıştık.

Yöntem: Endokrinoloji ve metabolizma kliniğine hiperkalsemi ile başvuran ve primer hiperparatiroidizm saptanan 71 hasta çalışmaya dahil edildi.

Bulgular: 71 paratiroid adenom hastasının ortalama yaşı 52.1 ± 13.4 idi. Hastaların %87,3'ü kadın (n=62) ve %12.7'si erkek (n=9) idi. Hastaların %35.2'si (n=25) asemptomatikti. Ameliyat öncesi paratiroid adenomu hastalarında serum intakt PTH düzeyi ile Ca/P oranı arasında pozitif korelasyon vardı. (p = 0,038, r = 0,258) Paratiroid adenomu olup birlikte vitamin D eksikliği olan hastalarda da ameliyat öncesi serum intakt PTH düzeyleri ile Ca/P arasındaki pozitif korelasyon korunmuştu (p = 0,037, r = 0,339).

Sonuç: Paratiroid adenomlu hastalarda PTH ile Ca/P oranı arasındaki pozitif korelasyon bozulmadan kalabilir. Bu korelasyon D vitamini eksikliği durumunda da bozulmayabilir.

Anahtar Kelimeler: paratiroid adenomu, D vitamini, kalsiyum

ABSTRACT

Objective: Primary hyperparathyroidism is a common calcium metabolism disorder. Patients with primary hyperparathyroidism are at risk for skeletal and renal damage.The presence of vitamin D deficiency may lead to difficulty in making a clear diagnosis. We reviewed the clinical charecteristics and laboratory findings of parathyroid adenoma patients in our center and tried to find a possible hallmark for parathyroid adenoma diagnosis regardless of vitamin D status of the patients.

Method: Patients who applied to the endocrinology and metabolism clinic with hypercalcemia and were diagnosed with primary hyperparathyroidism in the biochemical tests were included in the study.

Results: The mean age of the 71 parathyroid adenoma patients was 52.1 ± 13.4 years. 87.3% of the patients were female (n=62) and 12.7% were male (n=9). 35.2% (n=25) of patients were asymptomatic. There was a positive correlation between serum intact PTH level and Ca/P ratio in parathyroid adenoma patients before the surgery. (p = 0,038, r = 0,258) Positive correlation between serum intact PTH levels and Ca/P before surgery was also present in patients with parathyroid adenoma also in the presence of vitamin D deficiency (p = 0,037, r = 0,339).

Conclusion: The positive correlation between PTH and Ca/P ratio in patients with parathyroid adenoma may remain intact. This correlation may not be impaired in the case of vitamin D deficiency.

Keywords: parathyroid adenoma, vitamin D, calcium

INTRODUCTION

Primary hyperparathyroidism (PHPT); a clinical presentation of parathyroid adenomas, characterized by hypercalcemia of one or more glands with excessive parathormone secretion. Patients are usually asymptomatic. It is often diagnosed with elevated levels of calcium, which is investigated for other reasons (1). In symptomatic patients, pathological fractures, kidney stones, abdominal pain, dyspepsia, psychiatric disorders are the most frequent cases of referral to the hospital (2). The annual incidence of PHPT is 21/100000 - 51/100000 (3). It was found to be more frequent in women and the mean age of diagnosis was 33-63 (4). Symptoms are usually not directly related to serum calcium levels; but in cases where the serum calcium level increases rapidly, the patients are referred to the hospital more often with the mentioned symptoms. Parathyroidectomy is the only curative treatment for the disease. Parathyroidectomy reduces renal stone risk, improves bone mineral density (BMD) measurements, and reduces bone fracture risk (5). The classic symptoms and findings for PHPT are geographically diverse. "Osteoitis fibrosa cystica" is still common in developing and undeveloped countries. In developed countries, nephrolithiasis is the most common cause of symptomatic treatment (6-7). This difference is partly explained by the incidence of vitamin D deficiency (8-9). Vitamin D deficiency (25OHD level < 20 ng/mL) and insufficiency (25OHD 20-29 ng/mL) are common in primary PHPT. If vitamin D deficiency is present, larger parathyroid adenomas, higher PTH levels, increased bone turnover and more fractures can be seen (10). However definitions of vitamin D deficiency and insufficiency are still controversial and data on the applicability of these limit values to PHPT patients is unclear.

PHPT with vitamin D deficiency is considered to be associated with a higher adenoma weight, lower BMD, and more severe PHPT. However, there are also studies defending the hypothesis that the relationship between the vitamin D level and PHPT severity is not clear (11,12). We aimed to reveal the clinical, biochemical, and histopathological characteristics of parathyroid adenoma patients diagnosed in our clinic and to present some valuable results that we realized about this complex pathological process.

MATERIALS AND METHODS

Patients with primary hyperparathyroidism (n=71) were included in study between January 2010 and December 2016 in endocrinology and metabolism clinic. Patients under 18 years and patients with familial benign hypocalciuric hypercalcaemia, chronic kidney disesase, chronic liver disease, bisphosphonates and thiazide usage were excluded. Of the 71 patients with primary hyperparathyroidism were evaluated and had successful surgical treatment for parathyroid adenoma. Clinical, biochemical, radiological, scintigraphic and histopathological findings of 71 patients were retrospectively analyzed. Intact PTH, serum calcium, albumin, phosphorus, creatinine, alkaline phosphatase (ALP), Vitamin D, TSH, sT4, sT3, 24 hour urinary calcium and 24 hour urinary creatinine were examined. Renal functions were examined to exclude secondary hyperparathyroidism. For the serum calcium level, the albumin level corrected calcium formula was used: corrected calcium = total serum calcium [mg/dL] + 0.8 × (4-serum albumin [g/dL]). The following formula was used to calculate creatinine clearance (mL/min): (urine creatinine [mg/dL] × daily urine volume [mL]) / (serum creatinine [mg/dL] × 1440 [min]). The normal range for creatinine clearance was 75-115 mL / min for women and 95-145 mL / min for men. Abdominal USG results were categorized as normal, nephrolithiasis and nephrocalcinosis. Forearm, lumbar vertebra and femur neck BMD measurements were evaluated according to patients' T score. T score -1 and above were classified as normal, between -1 and -2.5 osteopenia and -2.5 and below as osteoporosis. X-ray hand evaluation results were grouped by presence of subperiosteal resorption. Laboratory and clinically diagnosed parathyroid adenomas patients were treated with surgery. The success of the operation was assessed intraoperatively by a 50% reduction in iPTH levels over 10 minutes according to Miami criteria (13). Frozen section confirmation was done intraoperatively and pathologic results confirmed as parathyroid adenomas. This study was conducted with the approval of Gaziantep University Clinical Research Ethics Committee, numbered 2016/291.

Statistycal Analysis: Normal distribution fitness of numerical data was tested by Shaphirowilk test. The Mann Whitney U test was used to compare normal non-dispersive variables in two groups, and the Kruskal Wallis test was used to compare two groups. The Paired Samples T test was used to compare normal distributed dependent variables, and the Wilcoxon test was used to compare normal non-distributed dependent variables. Relations between categorical variables The relationship between the normalized numerical variables and the Pearson correlation coefficient and the normal non-dispersive numerical variables were tested with the Spearman Rank correlation coefficient. SPSS 22.0 package program was used in the analyzes. P <0.05 was considered significant. Variables with normal distribution are shown by mean and standard deviation (Mean±SD).

Parathormone measurement: There are 3 immunoreactive structures that can be biochemically measured in the PTH structure, these are; 84 amino acid PTH molecules, amino-terminal (N-terminal) and carboxy-terminal (C-terminal) fragments. The primary method for measuring PTH is radioimmunoassay (RIA) and is known as first generation technique. "Immunometricassay (IMA)" includes second and third generation measurement techniques. In the RIA method, polyclonal antibodies interacting with the C-terminal portion are used. This measurement method, which does not include the N-terminal part, is also less sensitive and has now left its place to the IMA method. Measurement using IMA is called "intact PTH" in common use. In the third generation IMA technique, two different types of antibodies specific to the C-terminal and N-terminal ends are used. For this reason, much more accurate results are obtained. IMA is a much more sensitive and specific method than RIA, therefore intake PTH measurement with a normal range of 20-65 ng/l is used in our study (14-15).

RESULTS

The mean age of the 71 parathyroid adenoma patients was 52.1±13.4 years. 87.3% of the patients were female (n=62) and 12.7% were male (n=9). 35.2% (n=25) of patients were asymptomatic. Most frequent symptoms were weakness (23.9%) and bone pain (18.3%). (Table 1)

Table 1. Symptoms in Patients with Parathyroid Adenoma

Symptoms	Patients count (n)	(%)
No symptom	25	35.2
Fatigue	17	23.9
Bone pain	13	18.3
Stomachache	9	12.6
Dysuria	7	9.8
Total	71	100

40.8% of the patients with parathyroid adenomas did not have any comorbid disease. Hypertension (28.2%), diabetes mellitus (18.3%) and multinodular goiter (18.3%) were the most common comorbid diseases. (Table 2)

Table 2. Co-morbidities in Patients with Parathyroid Adenoma

Co-morbidity	Patient count (n)	(%)
Absent	29	40.8
Hypertension	20	28.2
Multinodular goiter	13	18.3
Diabetes mellitus	13	18.3
Papillary thyroid carcinoma	9	12.7
Dyslipidemia	7	9.9

In 53% of patients with PHPT, vitamin D levels were below 30 ng/ml. There was a weak positive correlation between serum intact PTH level and Ca/P ratio in parathyroid adenoma patients before the surgery. ($p = 0,038$, $r = 0,258$) Positive correlation between serum intact PTH levels and Ca/P before surgery was also present in patients with parathyroid adenoma also in the presence of vitamin D deficiency. ($p = 0,037$, $r = 0,339$) In contrast, there was no correlation found between serum intact PTH levels and Ca/P in patients with parathyroid adenoma in normal vitamin D status. ($p= 0,26$, $r = -0,343$) (Table 3)

Table 3. Correlation of Intact PTH Level with Serum Ca / P in The Presence of Vitamin D Deficiency or Normal Vitamin D Levels in Patients with Parathyroid Adenoma

				Ca/P1	PTH
Vitamin D <30 ng/ml	Spearman's Rho	Ca/P	r	1,000	.339*
			p	.	.037
			N	38	38
		PTH	r	.339*	1.000
			p	.037	.
			N	38	38
Vitamin D ≥30 ng/ml	Spearman's Rho	Ca/P	r	1.000	-.343
			p	.	.26
			N	33	33
		PTH	r	-.343	1.000
			p	.26	.
			N	33	33

Ca: Calcium, PTH: Parathormon, P: Phosphor
* $p < 0.05$ is significant

We found that 46% of the patients had Osteopenia, Osteoporosis in Lumbar or femur region. (Table 4)

Table 4. Clinical Features of Patients with Parathyroid Adenoma

Clinical features	N	%
Nephrolithiasis & Nephrocalcinosis	12	16
Osteopenia, Osteoporosis (Forearm)	10	14
Osteopenia, Osteoporosis (Lumbar &Femur)	33	46
Subperiosteal bone resorption phalanges	13	18

There was not a correlation among with adenoma weight and, calcium, alkaline phosphate, vitamin D and calciuria. All patients received a preoperative both sestamibi scan and USG of the neck. While no pathology was observed in 10 patients by USG, scintigraphy was detected pathology in all these patients. However, scintigraphy showed no uptake in 5 patients. The rate of adenoma detection by ultrasound is 87% (n =61) According to the 99mTc Sestamibi scintigraphy results, the rate of adenoma detection was 93.5% (n=66). There was a positive moderate correlation between preoperative PTH level and adenoma weight ($r=0,377$ $p=0,03$) and moderate negative correlation between phosphorus level and adenoma weight $r=-0,40$ $p=0,023$. (Table 5)

Table 5. Correlations Among with Adenoma Weight and Preoperative Laboratory Parameters

		PTH	Calcium	Phosphor	ALP	Vitamin D	Calciuria	Adenoma weight
PTH	r	1	.377[**]	-.179	.297[*]	-.372[**]	-.117	.377[*]
	p		.001	.154	.036	.010	.515	.030
Calcium	r	.377[**]	1	-.428[**]	.201	-.185	.019	.141
	p	.001		.000	.162	.214	.917	.435
Phosphor	r	-.179	-.428[**]	1	-.096	.222	.087	-.400[*]
	p	.154	.000		.506	.147	.636	.023
ALP	r	.297[*]	.201	-.096	1	-.325	-.048	-.243
	p	.036	.162	.506		.057	.809	.276
Vitamin D	r	-.372[**]	-.185	.222	-.325	1	.121	-.163
	p	.010	.214	.147	.057		.526	.438
Calciuria	r	-.117	.019	.087	-.048	.121	1	.169
	p	.515	.917	.636	.809	.526		.476
Adenoma weight	r	.377[*]	.141	-.400[*]	-.243	-.163	.169	1
	p	.030	.435	.023	.276	.438	.476	

* p < 0.05 is significant, ALP: Alkaline Phosphatase, PTH: Parathormon

DISCUSSION

PHPT is usually a clinical presentation of parathyroid adenoma rarely found in the presence of parathyroid carcinoma with hypercalcemia and excessive parathormone secretion from one or more glands. It is usually found more frequently in women and the average age at diagnosis is 33-63 years (4). The mean age of diagnosis of the patients was 52.1 years in our study. 87.3% of patients with parathyroid adenomas were female and 12.7% were male patients. In the literature, while the ratio of female to male is 3/1, in our study this rate was found to be higher in favor of women (7).

According to the study of Misgar et al., Nephrolithiasis / nephrocalcinosis (64.1%), bone pain (44.1%), abdominal pain (39%) and constipation (26%) were the most common cases of PHPT. In the study of Kaur et al., The most common cases of presentation were reported as nephrolithiasis (16%), pancreatitis (14%), fracture (3%), proximal muscle weakness (2%) (4). The most common cause of symptomatic PHPT in our study was fatigue (23.9%) and bone pain (18.3%). Fatigue is a non specific symptom and can be caused by many different situations. However, as seen in our study, frequent occurrence of vitamin D deficiency in our region may have reduced the incidence of nephrolithiasis and may trigger fatigue.

In patients with parathyroid adenoma, there was a positive correlation between serum Ca/P and intact PTH levels at first visit in regardless of vitamin D status. At least to our knowledge, previous studies on hyperparathyroidism have not shown any correlation between Ca/P and intact PTH levels in case of vitamin D deficiency. This result suggests that the correlation of Ca/P and intact PTH levels in regions where vitamin D deficiency is common may be a valuable predictive factor for predicting the diagnosis of parathyroid adenoma. Vitamin D deficiency and high PTH levels may cause increased bone turnover and more fractures including osteitis fibrosa systica as well as worse postoperative outcome (8,9,16). In our study, no osteitis fibrosa systica was found in any patient with vitamin D deficiency before surgery and all patients were curatively treated without any postoperative comorbidity. These finding contradicts the literature although the study was conducted in a region where vitamin D deficiency is common. Existing vitamin D deficiency may cause the level of serum calcium to fall to the normal range, which may lead to uncertainty in diagnosis (17). However, in our study, it is seen that Intact PTH level and Ca/P correlation did not have difficulty in predicting the diagnosis of parathyroid adenoma even if vitamin D deficiency was observed. But it may seem that this relationship is more complicated than these simple correlations. Indeed, in India, adenomal weights are much greater than in American patients with similar D vitamini deficiency, and adenomal weights are similar in Indian patients with and without vitamin D deficiency. It is also unclear whether there is a biochemical correlation with even more adenomal weight (6-18). There is also evidence patients with PHPT have lower levels of vitamin D than non-PHPT control subjects. Boudou et al. found D vitamine insufficiency in 93% of 145 patients who underwent parathyroidectomy for PHPT in France (10). The prevalence of PHPT may be underestimated in regions where vitamin D deficiency is common. These patients do not have clear follow-up parameters.

There are studies that say that the half-life of vitamin D in PHPT patients is shorter. Patients with high PHT levels may be experiencing vitamin D deficiency resulting from reduced vitamin D half-life. It is not easy to predict when low D vitamin is detected in a patient with PHPT, whether it is due to low intake of vitamin D or to PHPT itself. In another respect, patients with PHPT have an increased production of 1-25 (OH) Vitamin D. In vitro tests show that 1-25 (OH) D Vitamin D increases 25 (OH) Vitamin D conversion inhibition (19-20). This may seem like lack of vitamin D in laboratory tests. Considering these situations, we believe that correlation of these measurements can be used instead of calcium, phosphorus and intact PTH measurements alone. Our study showed that; Pathologically confirmed parathyroid adenomas patients with vitamin D deficiency still had correlation between intact PTH and Ca/P ratio.

FGF23 is a peptide hormone that is produced by osteocytes. FGF23 stimulates phosphaturia and inhibits PTH. Also FGF23 stimulates CYP24A1 and inhibits CYP27B1. Hence elevation in FGF23 level supreses 1,25 dihidroxyvitamin D level (21). In our study, the effect of FGF23 is unknown. We consider the absence of this effect as a limiting factor in the study. We think that it is important to keep in mind the FGF23 peptide hormone may be a confounding factor that can change the results while hiperparathyroidism assessed.

In conclusion; In patients with parathyroid adenomas, we think that correlation between PTH and Ca/P ratio will remain intact and clinician could use this correlation as a hallmark for differential diagnosis regardless of vitamin D status of the patients.

Main messages of the article;

• The diagnosis of parathyroid adenoma is difficult in case of vitamin D deficiency.

• We think that there is a need for new clues for the diagnosis of parathyroid adenoma other than the known biochemical changes.

• Correlation between PTH and Ca/P ratio will remain intact and clinician could use this correlation as a hallmark for differential diagnosis regardless of vitamin D status of the patients.

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