

Primary hyperparathyroidism due to parathyroid adenoma

Hande Koksal, MD, Osman Kurukahvecioglu, MD, Mustafa O. Yazicioglu, MD, Ferit Taneri, MD.

ABSTRACT

Objectives: To evaluate the clinical characteristics and outcome of patients with parathyroid adenoma.

Methods: We diagnosed and operated 54 patients with primary hyperparathyroidism in the Faculty of Medicine, Gazi University, Turkey from January 2000 to December 2004. In this study, 52 (96.2%) of these patients who had parathyroid adenoma were retrospectively evaluated.

Results: There were 46 female, and 6 male patients with a median age of 54.5 years (range, 18-87 years) at diagnosis. Preoperative mean serum level of calcium was 11.09 ± 0.9 mg/dL, while phosphorus was 2.3 ± 0.5 mg/mL, and parathyroid hormone (PTH) was 338.99 ± 416.43 pg/ml. Ultrasound imaging revealed parathyroid adenoma in 38 of the 52 patients (73%), while 27% of the patients were normal. In 29 (69%) of the 42 patients who had sestamibi scanning, results revealed parathyroid adenoma and in the others (31%), sestamibi scanning was normal. On the

postoperative period, the mean serum calcium level was 9.2 ± 0.74 mg/dL ($p=0.0001$ compared to preoperative level), phosphorus was 2.7 ± 0.39 mg/mL ($p=0.07$ compared to preoperative level), and PTH level was 41.01 ± 43.03 pg/ml ($p=0.0001$ compared to preoperative level). All patients were cured after operation, as determined by normalization in serum calcium levels in the postoperative period.

Conclusion: Parathyroid adenoma is the most common cause of primary hyperparathyroidism. Preoperative serum calcium and PTH levels are the most useful parameters for diagnosis. Preoperative screening methods and operative findings are not always correlated so the patients with high serum calcium and PTH should be planned for surgery, independent of radiological results. All patients were cured after operation, as determined by normalization in serum calcium levels in the postoperative period.

Saudi Med J 2006; Vol. 27 (7): 1034-1037

Primary hyperparathyroidism is a common endocrine disorder that can be surgically cured, and is an important cause of hypercalcemia. This condition is usually caused by a parathyroid adenoma or by primary hyperplasia of the glands. On rare occasions, it is caused by a carcinoma of parathyroids. Primary hyperparathyroidism is typically a disease of adults and is more common in women than in men. The elevated levels of parathyroid hormone (PTH) produce several changes, including excessive bone resorption, nephrolithiasis, hypertension, constipation, weakness, and psychiatric disorders.^{1,2}

The most common manifestation of primary hyperparathyroidism is an increase in the serum calcium level. The symptoms of primary hyperparathyroidism are nonspecific, reflecting multiorgan involvement with renal, gastrointestinal neuromuscular, cardiovascular, and central nervous system dysfunction, and are mostly reversible after surgery. In laboratory findings, serum PTH and calcium levels are inappropriately elevated, whereas PTH levels are low to undetectable in hypercalcemia caused by non-parathyroid disease. Preoperative imaging techniques such as sestamibi scintigraphy,

From the Department of General Surgery, Faculty of Medicine, Gazi University, Ankara, Turkey.

Received 30th January 2006. Accepted for publication in final form 9th April 2006.

Address correspondence and reprint request to: Dr. Hande Koksal, Chief Assistant in General Surgery, 7.Cadde 23.Sokak Kural Apartmanı, No: 5/12 Bahçelievler, 06500 Ankara, Turkey. Tel. +90 (505) 3194257. E-mail: drhandeniz@yahoo.com

high-resolution ultrasound, and development of the intraoperative PTH assay are useful for focused parathyroid pathology.^{1,3}

In 80-90% of cases with hyperparathyroidism, the parathyroids harbor a solitary adenoma. Thus, we aimed to evaluate the clinical characteristics and outcome of patients with parathyroid adenoma.

Methods. Fifty-four patients were diagnosed and operated upon for primary hyperparathyroidism in our center at Gazi University, Ankara, Turkey from January 2000 to December 2004. Fifty-two (96.2%) of these patients who had parathyroid adenoma were retrospectively evaluated in this study. Two patients with parathyroid hyperplasia were excluded. The patients were routinely evaluated by physical examination and laboratory tests, including a complete blood count, renal function tests, preoperative and postoperative serum calcium and PTH values, and urinalysis. Localization of the parathyroid adenoma was determined by sestamibi scintigraphy, ultrasound, or neck magnetic resonance imaging. The treatment strategy was surgery.

The Statistical Package for Social Sciences program was used for data analysis. Patient characteristics were summarized using descriptive statistics: mean \pm SD was used for the expression of continuous variables. Comparison of the pre- and postoperative values of calcium, phosphorus, and PTH were performed using paired samples t test.

Results. During the study period, 54 patients underwent parathyroid surgery, 52 of them were diagnosed with parathyroid adenoma (96%). The clinical features of the 52 patients are given in **Table 1**. There were 46 females and 6 males with a median age of 54.5 years (range, 18-87 years) at the time of diagnosis. Greatest frequency of parathyroid adenoma (83%) was observed in patients between 40 and 70 years of age. No patient had a history of neck radiotherapy.

In 22 patients (37%), hypercalcemia was detected in routine control without any symptoms. The major presenting symptoms or signs were weakness (36%), palpable nodule (15.4%) and palpitation (5.8%). Three patients had nephrolithiasis (5.8%). There were 37 patients with significantly high serum calcium levels. Other patients have calcium levels just above the normal limits. In all patients except one, high serum PTH levels were determined. Preoperative mean serum level of calcium (n=52) was 11.09 ± 0.9 mg/dL (range, 8.2-10.6 mg/dL), phosphorus level (n=52) was 2.3 ± 0.5 mg/mL (range, 2.5-4.5 mg/dL),

Table 1 - Clinical features of 52 patients with parathyroid adenoma.

Characteristics	N (%)
Gender	
Female	46 (89)
Male	6 (11)
Age (median) 18-87 years (median, 54.5)	
20-40	5 (9)
40-70	43 (83)
>70	4 (8)
Localization (according to surgery)	
Right superior	3 (6)
Left superior	1 (2)
Right inferior	25 (48)
Left inferior	21 (40)
Intrathyroidal	1 (2)
Bilateral inferior	1 (2)

and PTH (n=52) was 338.99 ± 416.43 pg/mL (range, 12-75 pg/mL).

Neck ultrasound revealed that 38 of 52 patients (73%) had parathyroid adenoma. In others (27%) neck ultrasound examinations was normal. Sestamibi scanning was performed in 42 of 52 patients. In 29 of 42 patients (69%) sestamibi scanning revealed parathyroid adenoma and in the others (31%), sestamibi scanning was normal. The sensitivity of ultrasound was 73% while it was 69% for sestamibi scanning in our study. Positive predictive value for both imaging studies was 100%. Neither ultrasound examination nor sestamibi scanning could find any pathology in 11 patients.

All patients were operated under general anesthesia. Bilateral neck exploration was performed for each patient independent of imaging studies, and afterwards parathyroidectomy was carried out. Approximately 88% of the adenomas were located in the inferior parathyroid glands (**Table 1**). On histopathological examination, all patients were diagnosed as parathyroid adenoma, one of whom had synchronous adenomas.

In the postoperative period, there were 5 patients with serum calcium levels below 8.2 mg/dL (9.6%). Five patients had high PTH levels (9.6%) postoperatively, and 3 had serum calcium levels higher than 10.6 mg/dL, whereas at the first month follow-up, the levels of serum calcium and PTH of the patients were within normal ranges. On the second postoperative day, mean serum level of calcium (**Figure 1**) was 9.2 ± 0.74 mg/dL ($p=0.0001$ compared to preoperative level), phosphorus level was 2.7 ± 0.39 mg/mL ($p=0.07$ compared to preoperative level), and

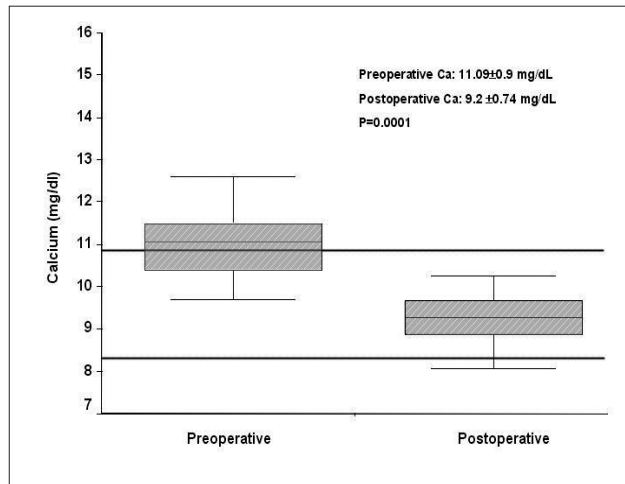


Figure 1 - Serum levels of calcium during the preoperative and postoperative period.

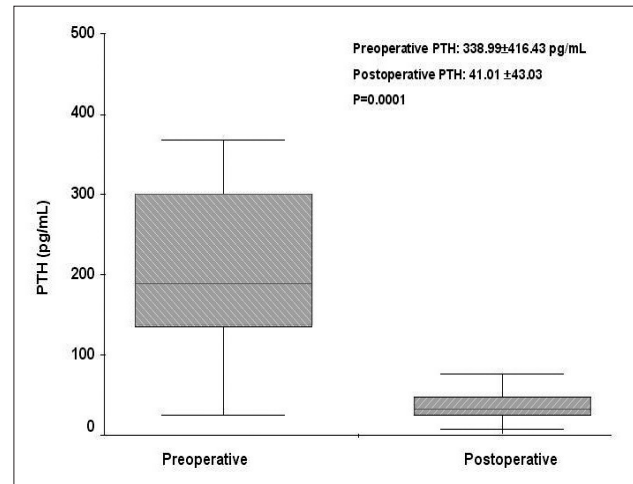


Figure 2 - Serum levels of PTH during the preoperative and postoperative period.

PTH was 41.01 ± 43.03 pg/ml ($p=0.0001$ compared to preoperative level) (Figure 2).

All patients were cured after operation, as determined by normalization in serum calcium levels in the postoperative period.

Discussion. Primary hyperparathyroidism is a relatively common endocrine disease with an incidence higher than 1/1000. It is characterized by hypercalcemia and elevation of PTH levels. The incidence is variable, being more frequent in women in the perimenopausal period.^{4,5} Most of them are parathyroid adenomas (83-98%).^{6,7} In one study,⁸ exposure to ionizing radiation to the cervical spine in adult age seems to be associated with an increased risk of developing parathyroid adenomas was reported. In our center, 54 parathyroid operations were performed in 5 years, and 52 (96%) were diagnosed as parathyroid adenoma, and 2 (4%) were hyperplasia. The female to male ratio was 46:6. None of the patients had a history of neck radiotherapy.

The symptoms frequently reflect multi-organ involvement such as gastrointestinal, renal, cardiovascular, neuromuscular and central nervous system. In Silverberg and Bilezikian's study,⁵ common clinical manifestations included bone pain, weakness or fatigue, fracture of the long bones, abdominal pain, polyuria, and psychiatric manifestations were reported. Hypertension was observed in 42% and a palpable nodule in the neck was seen in 19% of the patients. Recently, frequency of asymptomatic primary hyperparathyroidism has increased due to automatized calcium determinations.⁷ In our patients, major presenting symptoms or signs were

weakness and palpitation. Twenty-two patients had no complaints, and hypercalcemia was determined in routine controls. Three patients had nephrolithiasis.

Biochemical features in primary hyperparathyroidism include hypercalcemia and elevation of PTH.^{1,3-6} Hypophosphatemia or hyperphosphatemia can also be determined.⁶ After surgery, calcium levels are usually within normal limits. However, post-operatively hypocalcemia can also be detected. Patients with primary hyperparathyroidism who underwent subtotal parathyroidectomy had significantly lower postoperative calcium levels than patients who had a single or double adenomas removed as reported by Mittendorf et al.⁹ Preoperatively, there were 37 patients with high serum calcium levels, and the others had calcium levels just above the upper limits. After surgery, 10% of the patients had hypocalcemia and 10% of the patients had high serum PTH levels. Three of the patients had high serum calcium levels. At the first month follow-up, the high levels of serum calcium and PTH were within normal limits.

Ultrasound is frequently the preferred modality for localization of abnormal parathyroid. The sensitivity of ultrasound was reported as 86.9%, while positive predictive value was 89.1%.⁹ Sestamibi scanning is also used for detecting parathyroids pathology. However, false negative results limit the efficacy of sestamibi scanning for parathyroid localization. The false-negative rate of sestamibi for the diagnosis of parathyroid adenoma is 23.3%.^{10,11} Sestamibi had a sensitivity of 83.3% and positive predictive value of 87.1%. The simple combination of ultrasound with sestamibi had a sensitivity of 82.1% and a

positive predictive value of 92%, a little different from sestamibi alone.¹² In Merlino's et al study,¹³ sestamibi parathyroid imaging is limited by a 22% false negative rate, and is less accurate for detecting abnormal parathyroid tissue in patients with small adenomas, multiglandular disease, superior adenomas, or preoperative normocalcemia. In our study, ultrasound revealed parathyroid adenoma in 73% of the patients. However, parathyroid adenoma could not be determined by ultrasound in 27% of the patients. Of the 42 patients who performed sestamibi scanning, 69% have parathyroid adenoma and 31% of these patient have normal sestamibi scanning result. Both ultrasound and sestamibi scanning were performed in 42 patients, and in 11 neither of these revealed adenoma. In our study, the sensitivity of ultrasound was 73% while sestamibi scanning was 69%.

Surgery is the definitive treatment in parathyroid adenomas. It is important to assess surgical criteria in asymptomatic patients. Successful treatment of this disease depends on a highly specialized team of parathyroid surgeons.^{1,2,5} The minimally invasive radioguided parathyroidectomy is a safe and efficacious method. The surgical approach of choice should also involve the bilateral exploration of the neck.

In summary, the most important cause of primary hyperparathyroidism is parathyroid adenoma. It is usually characterized by hypercalcemia and elevation of PTH levels. Parathyroid adenomas sometimes cannot be determined with both ultrasound and sestamibi scanning as in our patients, so in patients with high serum calcium and PTH levels, bilateral neck exploration followed by parathyroidectomy should be performed independent of the imaging studies even if the patients are asymptomatic. The other approach is using complementary techniques such as intraoperative ultrasonography and rapid parathyroid hormone assay, to ensure a successful excision if a limited surgical procedure is planned. Surgery is the definitive treatment, and recurrence risk is very low.

References

1. Lal G, Clark OH. Thyroid, parathyroid and adrenal. In: Brunicaledi FC, Andersen DK, Billiare TR, Dunn DL, Hunter JG, Pollock RE. editors. Schwartz's Principles of Surgery. 8th ed. New York (NY): McGraw-Hill; 2005. p. 1395-1471.
2. Russell C. Unilateral neck exploration for primary hyperparathyroidism. *Surg Clin N Am* 2004; 84: 705-716.
3. Marx SJ. Diseases of bone and bone mineral metabolism. In: Goldman L, Bennett JC, editors. Cecil Text Book of Medicine. 21st ed. Philadelphia (PA): WB Saunders; 2000. p. 1383-1389.
4. Fischer JA. Asymptomatic and symptomatic primary hyperparathyroidism. *Clin Investig* 1993; 71: 505-518.
5. Silverberg SJ, Bilezikian JP. Asymptomatic primary hyperparathyroidism: a medical perspective. *Surg Clin North Am* 2004; 84: 787-801.
6. Bhansali A, Masoodi SR, Reddy KS, Behera A, das Radotra B, Mittal BR, et al. Primary hyperparathyroidism in north India: a description of 52 cases. *Ann Saudi Med* 2005; 25: 29-35.
7. Mendoza-Zubieta V, Zamudio-Villarreal JF, Pena-Garcia JF, Marin-Mendez A, Martinez-Martinez L, Mercado-Atri M. Primary hyperparathyroidism: a report of 67 cases. The experience of 5 years at the IMSS Centro Medico Nacional Siglo XXI Specialties Hospital. *Cir Cir* 2003 71: 363-368.
8. Rasmuson T, Damber L, Johansson L, Johansson R, Larsson LG. Increased incidence of parathyroid adenomas following X-ray treatment of benign diseases in the cervical spine in adult patients. *Clin Endocrinol (Oxf)* 2002; 57: 731-734.
9. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. *Am Surg* 2004; 70: 114-119.
10. Ghaheri BA, Koslin DB, Wood AH, Cohen JI. Preoperative ultrasound is worthwhile for reoperative parathyroid surgery. *Laryngoscope* 2004; 114: 2168-2171.
11. Rodriguez-Carranza S, Caceres M, Aguilar-Salinas CA, Gomez-Perez FJ, Herrera MF, Pantoja JP, et al. Localization of parathyroid adenomas by (99m)Tc-sestamibi scanning: upper neck versus lower neck lesions. *Endocr Pract* 2004; 10: 472-477.
12. Hajioff D, Iyngkaran T, Panagamuwa C, Hill D, Stearns MP. Preoperative localization of parathyroid adenomas: ultrasonography, sestamibiscintigraphy, or both? *Clin Otolaryngol Allied Sci* 2004; 29: 549-552.
13. Merlino JI, Ko K, Minotti A, McHenry CR. The false negative technetium-99m-sestamibi scan in patients with primary hyperparathyroidism: correlation with clinical factors and operative findings. *Am Surg* 2003; 69: 225-229.
14. Sozio A, Schietroma M, Franchi L, Mazzotta C, Cappelli S, Amicucci G. Parathyroidectomy: bilateral exploration of the neck vs minimally invasive radioguided treatment. *Minerva Chir* 2005; 60: 83-89.