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Parathyroidectomy: Whom and when?

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Parathyroidectomy: Whom and when? Hyperparathyroidism (HPT) is common in patients on dialysis, and parathyroidectomy (PTx) is often required. We present a retrospective, descriptive analysis of data corresponding to 148 patients on dialysis undergoing PTx due to severe refractory HPT (PTH 1401 ± 497 pg/mL, Ca 10.6 ± 0.8 mg/dL, P 6.9 ± 1.7 mg/dL). Demographic data were compared with those recorded in 309 patients on dialysis not subjected to PTx who were managed at the same hospital. In the PTx group, the factors age (49.3 ± 14 years), male gender (48.6%), and diabetes (0.7%) were significantly lower than in the non-PTx group (61.5 ± 14.9 years, male gender 59%, diabetes 19.4%), while time on dialysis was longer (8.6 ± 5.8 vs. 5.5 ± 5.4 years). In 129 of the study patients (87.4%), four or more glands were identified, and total PTx plus autotransplantation (AT) in the forearm was performed. In the remaining 19 patients, two to three glands were identified, and AT was not undertaken. Four of the 19 patients were successfully operated on again for persistent HPT, seven showed PTH levels <250 pg/mL, and eight maintained severe HPT. Perioperative complications included one death due to cardiac insufficiency, two repeat operations due to bleeding, and one patient with chronic hoarseness. Hospital stay was prolonged in 20% of patients due to a hungry bone syndrome. Among those patients with PTx and AT, HPT recurred in 21 patients (16.2%) at 3.1 ± 2.3 years. In 13 of these patients, autograft was removed at 7.5 ± 2.9 years. Serum calcium and phosphate levels improved after PTx, and these results were maintained for 5 years (9.6 ± 0.8 and 4.2 ± 1.2 mg/dL, respectively). In conclusion, PTx with AT is a safe option for the treatment of severe HPT that is accompanied by low morbidity and mortality and a good outcome. Medical treatment should not be prolonged at the expense of long repeated bouts of hypercalcemia and/or hyperphosphatemia with their irreversible consequences.

Over the past twenty years, secondary hyperparathyroidism has been mainly managed by combination treatment with calcium salts and calcitriol [1]. This approach leads to a positive calcium balance and enhanced intestinal absorption of calcium and phosphate. In its initial stages, this treatment is effective, but as secondary hyperparathyroidism progresses, the gland becomes resistant and the patient starts to present with hypercalcemia and/or hyperphosphatemia [2]. The association between high calcium and phosphate levels and higher morbidity and mortality, especially cardiovascular, has been demonstrated in patients with chronic renal insufficiency, and presents with values of the calcium x phosphate product >55 mg^2/dL^2, which were considered safe [3] until recently.

Further therapeutic options, such as vitamin D metabolites, calcimimetics, or aluminium- and calcium-free phosphate-binding agents have not been able to satisfactorily resolve the problem or are still at an early stage of development [4–7].

Parathyroidectomy (PTx) is the treatment of choice in patients with severe HPT and is the safest option when medical approaches have failed [8]. Correct evaluation of a lack of response to treatment is essential to avoid unnecessary risk to the patient. The surgical techniques employed and subsequent management are crucial factors for outcome. The last few years have also seen alternative strategies to surgical PTx, including percutaneous intraglandular ethanol or calcitriol injection [9].

The aim of this study was to evaluate, in terms of surgical indications and their early and late results, data corresponding to a series of patients from our center with severe HPT who were subjected to total PTx with autotransplantation (AT).

METHODS

The study population selected was treated at our dialysis unit and two of its satellite hemodialysis centers, where there are presently 329 patients on hemodialysis (HD), and 30 on peritoneal dialysis (PD). We retrospectively examined data derived from 148 patients (145 on HD, 3 on DP) who had been parathyroidectomized due to severe HPT over the period of January 1990 to March 2002. The demographic characteristics of the study pa-

Key words: parathyroidectomy, hyperparathyroidism recurrence, hyperparathyroidism persistence.

Table 1. Demographic data

	Patients with PTx $N = 148$	Control $N = 309$
Age *years*	49 ± 14	61.5 ± 14.9[a]
Gender *% male*	48.6%	59%[b]
Time on dialysis *years*	8.6 ± 5.8	5.5 ± 5.4[a]
Diabetic	0.7%	19.4%[a]
Nondiabetic	99.3%	80.6%

Data were performed using Student *t* test.
[a] $P < 0.001$
[b] $P < 0.05$

tients were compared to those of patients undergoing dialysis at the same centers but who did not undergo surgical treatment (Table 1). All the patients had been treated with oral or intravenous calcitriol, calcium salts, and aluminum hydroxide. PTH levels were determined by RIA DPC Immulite 2000 (Diagnostic Products Corporation, Los Angeles, CA, USA) (normal range, 12 to 60 pg/mL).

Surgery was indicated in patients with persistently high PTH levels (>700 pg/mL) and hypercalcemia and/or hyperphosphatemia, as well as in cases of transient PTH decrease associated with hypercalcemia and/or hyperphosphatemia, which required the repeated withdrawal of treatment. In four patients with spontaneous breakage of the quadriceps tendon, immediate surgery was indicated.

The surgical technique of choice was total PTx plus forearm AT, whereby fragments of the least nodular gland, as determined by microscopy, were selected for AT. Surgery was exhaustive, with excision of the fatty tissue surrounding the glands, resection of the thymus remains, and bilateral opening of carotid sheaths.

Statistical analysis

Comparison of non-paired data between the two groups was performed by the Student *t* test. Qualitative variables were compared by the chi-square test. Analysis of variance (ANOVA) was used to compare paired data. The level of significance was set at $P < 0.05$.

RESULTS

Patients selected for PTx were significantly younger and had been on dialysis for a longer duration. There was an increased proportion of women and lower incidence of diabetes in the PTx group than in the non-PTx group (Table 1).

In 129 patients (87.7%), four or more glands were identified; these patients were subjected to total PTx plus AT. In the remaining 19 patients (12.3%), only 3 (17 patients) or 2 glands (two patients) were identified, and AT was not performed. Seven of these patients showed PTH levels <250 pg /mL. An ectopic mediastinal gland

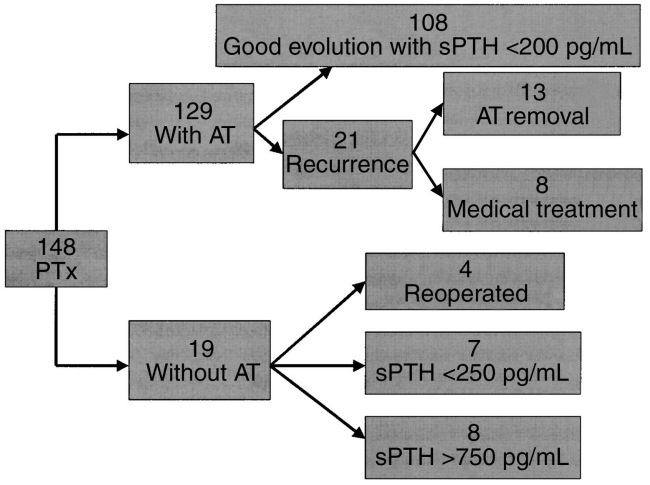

Fig. 1. Evolution of parathyroid function after PTx in the 129 patients (top) in whom 4 or more glands were identified (PTx and AT), and in the 19 patients (bottom) with only 3/2 glands identified at surgery (PTx without AT).

was subsequently identified by 99mTc-MIBI scintigraphy in another six patients, four of whom were operated on again successfully. Eight patients showing PTH >700 pg/mL were not operated on again for medical reasons or at the patient's request (Fig. 1).

The number of complications related to surgery was low: one death due to heart failure, two repeated interventions due to bleeding, and one patient with chronic hoarseness. Twenty percent of the patients presented with hungry bone syndrome (Ca <8.0 mg/dL for over 8 days, despite high doses of oral or intravenous calcium and treatment with calcitriol). These patients were significantly younger than the remaining patients, and presurgery PTH and alkaline phosphatase values were significantly higher (data not shown).

Seventy-nine point five percent of glands showed nodular hyperplasia, which was multinodular in 83.5%. Mean glandular weight was 1.18 ± 1.55 g. In the remaining 20.5%, hyperplasia was diffuse, with the mean weight of the glands being 0.628 ± 0.784 g. Glandular asymmetry was observed in 77% of the patient series.

Mean length of follow-up was 5.2 ± 3.9 years. At the time of writing, 56 patients (37.8%) were still on dialysis, 30 (20.2%) had received a transplant, 41 patients had died (28.7%) 3.5 ± 2.9 years after surgery, and the remaining 21 patients (13.8%) had been lost to follow-up.

Table 2 shows the patients' analytical profiles, which indicate good serum calcium and phosphate control with normalization of the calcium x phosphate product five years after surgery. All the patients are still under treatment with calcium salts and/or calcitriol.

Recurrence of HPT (PTH >250 pg/mL) occurred in 21 patients (16%) at 3.1 ± 2.3 years. In 13 patients,

Table 2. Analytical changes post-PTx

	Basal $N = 148$	1 year $N = 89$	2 years $N = 75$	5 years $N = 69$
PTH *pg/mL*	1401 ± 497[a]	154 ± 246	100 ± 132	249 ± 480
Ca *mg/dL*	10.6 ± 0.8[a]	9.5 ± 0.9	9.6 ± 0.8	9.6 ± 0.8
P *mg/dL*	6.9 ± 1.7[a]	5.2 ± 1.2	5.0 ± 1.8	4.2 ± 1.2
Ca x P mg^2/dL^2	61.5 ± 23.1[a]	46.5 ± 19.5	46.3 ± 15.4	42.3 ± 14.1
AP Ul	737 ± 519[a]	253 ± 130	215 ± 88	232 ± 159

The difference was found to be significant by analysis of variance (ANOVA).
[a] $P < 0.001$

the AT was removed under local anesthesia. Nodular hyperplasia was observed in all cases.

At 7.5 ± 2.9 years, 21 patients persistently showed PTH levels <30 pg/mL with no apparent clinical consequences.

DISCUSSION

In our series, PTx with AT proved effective and safe in patients in whom medical treatment had failed, particularly in terms of improving calcium and phosphate control. There is growing evidence of the importance of the early identification of patients in whom treatment is not only ineffective, but which also leads to devastating consequences, including increasing morbidity and mortality especially at the cardiovascular level [3]. PTH has a series of direct effects on cardiac function, hypertrophy, myocardial fibrosis, ischemia, and atherosclerosis [10]. Recent studies have demonstrated a relationship between myocardial, valve, coronary, and vascular calcifications with an enhanced Ca x P product and raised intake of calcium salts [3, 10–14].

Indicators of medical treatment failure are mostly biochemical. A lack of response is defined as persistently high serum PTH levels (8 to 10 times above normal values) in the presence of hypercalcemia and/or hyperphosphatemia, or when there is transient PTH decrease accompanied by repeated episodes of hypercalcemia and/or hyperphosphatemia, requiring the repeated interruption of treatment. In this situation, treatment should not be continued for longer than 6 to 8 months to avoid irreversible complications [8, 15].

Isolated high PTH values are not, in themselves, an indication for surgery but may predict the outcome of medical treatment. Rodríguez et al [16] examined 50 patients on HD treated with calcitriol and defined a response to treatment as a 40% decrease in basal PTH levels at 2 months. In patients with PTH values above 750 and 1200 pg/mL, the likelihood of an adequate response is 50% and 20%, respectively.

Clinical findings are important for establishing when surgery is indicated, though correlation with PTH values is highly variable. Bone pain, myopathy, metastatic calcification, and pruritus are the most common symptoms [17]. Four of our patients suffered spontaneous breakage of the quadriceps tendon. When associated with severe HPT, calciphylaxia is an urgent indication for surgery [17]. Surgery leads to improved bone pain, muscle weakness, and pruritus. Soft tissue, but not vessel, calcification subsides [17, 18].

Risk factors associated with HPT include: black race, younger age, female gender, longer time on dialysis, and hemodialysis versus peritoneal dialysis [19–22]. In our series, patients requiring PTx were significantly younger, and the percentage of women and time on dialysis were greater than the mean corresponding to all patients managed at our center. The incidence of diabetes was low, as described in another series [23].

There is still much dispute over the most efficient surgical technique in terms of avoiding both recurrence and the development of adynamic bone disease. Three procedures are employed in current clinical practice: total PTx, total PTx with AT, and subtotal PTx (whereby a fragment of the gland is left in situ) [8]. Our procedure of choice was total PTx with AT in the forearm. The recurrence rate was 16%. Tominaga et al [18] reported recurrence rates of 10%, 20%, and 30% at 1, 5, and 7 years, respectively, in a series of 1053 patients treated with an operative procedure similar to ours. In a review of 1299 cases published until 1990 (920 total PTX plus AT, 379 subtotal PTX), Rothmund observed no difference in the outcome of either technique. Similar findings have been reported by others [24, 25, 26].

In patients with an AT, recurrence depends in part on maintaining the uremic environment and the characteristics of the transplanted tissue. Microscopy appearance is of limited use when selecting the tissue for implant, although some investigators have obtained good results using a stereomagnifier system [27]. It has been proposed that the autograft should be taken from the smallest gland [18], and this is our current policy. Glands showing a volume larger than or 500 mm^3, or any diameter greater than 1 cm on ultrasonography, are associated with 80% nodular transformation, rendering them treatment resistant [18]. Glandular size is currently accepted as an indication for surgery.

When HPT recurs, the PTH gradient between each arm helps to identify whether the excess PTH is associ-

ated with the graft or with ectopic parathyroid tissue [28]. Treating a recurrence is easier when the patient has undergone AT rather than subtotal PTx. In our series, the forearm autograft was removed under local anesthesia in an outpatient setting. In some cases, surgery was laborious due to infiltration of parathyroid tissue in the muscle. All the grafts removed presented with nodular transformation.

In patients not on the transplant waiting list who show little adherence to treatment, some authors advocate total PTx plus cryopreservation of glandular tissue for subsequent autografting, if necessary [29, 30]. The common existence of ectopic parathyroid tissue and scarce clinical relevance of hypoparathyroidism in patients on dialysis lends support to this practice, although only a few patients have been monitored thus far. In 21 of our patients, PTH levels as low as <30 pg/mL persisted for 5 to 10 years with no apparent clinical consequences.

In conclusion, in patients with severe HPT, total PTx with AT appears to be safe and effective when nonsurgical treatment fails. In the hands of an experienced surgeon, operative morbidity is low. The procedure should be performed as early as possible to avoid the adverse, irreversible effects of prolonged hypercalcemia/hyperphosphatemia, and to improve osteoarticular symptoms. Subsequent management should be cautious, avoiding both relapse and exposure to inadequate levels of serum calcium and phosphate in patients with possible low bone turnover.

REFERENCES

1. Goodman WG: Recent developments in the management of secondary hyperparathyroidism. *Kidney Int* 59:1187–1201, 2001
2. Fernández Giráldez E: Dilemas del presente y perspectivas de futuro en el tratamiento de la osteodistrofia renal. *Nefrologia* XX(Suppl 3):41–51, 2000
3. Block GA: Prevalence and clinical consequences of elevated Ca x P product in hemodialysis patients. *Clin Nephrol* 54:318–324, 2000
4. Steddon S, Schroeder N, Cunnigham J: Vitamin D analogues: How do they differ and what is their clinical role? *Nephrol Dial Transplant* 16:1965–1967, 2001
5. Sherrard DJ: Manipulating the calcium receptor. *J Am Soc Nephrol* 13:1124–1125, 2002
6. Malluche H, Mawad H: Management of hyperphosphataemia of chronic kidney disease: Lessons from the past and future directions. *Nephrol Dial Transplant* 17:1170–1175, 2002
7. Chertow GM, Burke TJ, Dillon MA, *et al*: Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. *Nephrol Dial Transplant* 14:2709–2714, 1999
8. Locatelli F, Cannata-Andía JB, Drüeke T, *et al*: Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia. *Nephrol Dial Transplant* 17:723–731, 2002
9. Fukagawa M, Kitaoka M, Tominaga Y, *et al*: Selective percutaneous ethanol injection therapy (PEIT) of the parathyroid in chronic dialysis patients—the Japanese strategy. *Nephrol Dial Transplant* 14:2574–2577, 1999
10. Rostand SG, Drüëke TB: Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 56:383–392, 1999
11. Goodman WG, Goldin J, Kuizon BD, *et al*: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342:1478–1483, 2000
12. Raggi P: Detection and quantification of cardiovascular calcifications with electron beam tomography to estimate risk in hemodialysis patients. *Clin Nephrol* 54:325–333, 2000
13. Guerin AP, London GM, Marchais SJ, Metivier F: Arterial stiffening and vascular calcification in end stage renal disease. *Nephrol Dial Transplant* 15:1014–1021, 2000
14. Kimura K, Saika Y, Otani H, *et al*: Factors associated with calcification of the abdominal aorta in hemodialysis patients. *Kidney Int* (Suppl 71):S238–241, 1999
15. Schomig M, Ritz E: Management of disturbed calcium metabolism in uremic patients. 2. Indications for parathyroidectomy. *Nephrol Dial Transplant* 15 (Suppl 5):S25–S29, 2000
16. Rodríguez M, Caravaca F, Fernandez E, *et al*: Parathyroid function as a determinant of the response to calcitriol treatment in the hemodialysis patient. *Kidney Int* 56:306–317, 1999
17. Llach F, Velasquez Forero F: Secondary hyperparathyroidism in chronic renal failure: Pathogenic and clinical aspects. *Am J Kidney Dis* 38(Suppl 5):S20–S33, 2001
18. Tominaga Y, Uchida K, Haba T, *et al*: More than 1,000 cases of total parathyroidectomy with forearm autograft for renal hyperparathyroidism. *Am J Kidney Dis* 38(Suppl 1):S168–171, 2001
19. Gupta A, Kallenbag LR, Zasuwa G, Divine GW: Race is a major determinant of secondary hyperparathyrodisim in uremia. *Am J Soc Nephrol* 11:330–334, 2000
20. Chertow GM, Plone M, Dillon MA, *et al*: Hyperparathyroidism and dialysis vintage. *Clin Nephrol* 54:295–300, 2000
21. Malberti F, Marcelli D, Conte F, *et al*: Parathyroidectomy in patients on renal replacement therapy: An epidemiologic study. *J Am Soc Nephrol* 12:1242–1248, 2001
22. Torres A, Lorenzo V, Hernandez D, *et al*: Bone disease in predialysis, hemodialysis and CAPD patients: Evidence to a better response to PTH. *Kidney Int* 47:1434–1442, 1995
23. Inaba M, Okuno S, Nagasue K, *et al*: Impaired secreation of parathyroid hormona is coherent to diabetic hemodialyzed patients. *Am J Kidney Dis* 38(Suppl 1):S139–142, 2001
24. Rothmund M, Wagner P, Schark C: Subtotal parathyroidectomy and autotransplantation in secondary hyperparathyroidism: A randomized trial. *World J Surg* 15:745–759, 1991
25. Gasparri G, Camandona M, Abbona GC, *et al*: Secondary and tertiary hyperparathyroidism: Causes of recurrent disease after 446 parathyroidectomies. *Annals of Surg* 233:65–69, 2001
26. Maxwell PH, Winearls CG: Recurrence of autonomous hyperparathyroidism in dialysis patients. *Nephrol Dial Transplant* 12: 2195–2200, 1997
27. Neyer U, Hoerandner H, Haid A, *et al*: Total parathyroidectomy with autotransplantation in renal hyperparathyroidism: Low recurrence after intraoperative tissue selection. *Nephrol Dial Transplant* 17:625–629, 2002
28. Walgenbach S, Hommel G, Junginger T: Prospective evaluation of parathyroid graft function in patients with renal hyperparathyroidism after total parathyroidectomy and heterotopic autotransplantation by measurement of the intact parathyroid hormone concentrations in both antecubital veins. *Eur J Surg* 165:343–350, 1999
29. Stracke S, Jehle P, Sturm D, *et al*: Clinical course after total parathyroidectomy without autotransplantation in patients with end-stage renal failure. *Am J Kidney Dis* 33:304–311, 1999
30. De Francisco A, Fernández Fresnedo G, Rodrigo E, *et al*: Parathyroidectomy in dialysis patients. *Kidney Int* 61(Suppl 80):S161–166, 2002