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Dynamics of Parathyroid Hormone Secretion After Total Parathyroidectomy and Autotransplantation

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Abstract
Background Secondary hyperparathyroidism is a common complication in uremic patients. Total parathyroidectomy combined with partial autotransplantation into brachioradialis muscle has been the preference among the options for surgical treatment. This study was designed to evaluate the reserve and ability of suppression of autotransplanted parathyroid tissue using dynamics tests.
Methods We studied, prospectively, 12 patients in recent (RP) and late (LP) postoperative of total parathyroidectomy with autotransplantation. For analysis of the secretory reserve capacity, we induced hypocalcemia by ethylenediaminetetraacetic acid (EDTA) infusion. Furthermore, for analysis of the ability for parathyroid hormone (PTH) suppression, the hypercalcemia test was used, by intravenous administration of calcium in LP.
Results In RP, there was a decrease in the average serum levels of PTH, phosphorus, and alkaline phosphatase, which ranged from 13 to 231 (87 ± 65) pg/ml, 2.3 to 6.2 (3.3 ± 1.1) mg/dl, and 77 to 504 (250 ± 135) U/L, respectively, similar to that observed in LP. The analysis of the average curve of variations in PTH during testing of the stimulus with EDTA showed lack of secretion in RP and partial response in LP. Impaired suppression ability of the graft in LP was observed in the test with intravenous calcium.
Conclusions Total parathyroidectomy followed by partial autotransplantation was effective in reducing PTH serum levels in patients with terminal kidney disease. The elevation of serum calcium during the suppression test was not able to inhibit the autograft gland secretion of PTH. The assessment of parathyroid graft function demonstrated an inability to respond to the stimulus of hypocalcemia induced by EDTA, although there was a partial recovery, in late postoperative period.

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Introduction

Secondary hyperparathyroidism has been a common complication of renal disease. Most patients are properly treated with medication and diet. The phosphorus restrictive diet associated with chelating agents can help to control hyperphosphatemia, and calcitriol administration, intended to supply its endogenous deficiency, has satisfactory effect on the parathyroid hormone (PTH) inhibition. Calcium administered with meals also helps to increase the serum calcium levels and reduces intestinal phosphorus absorption. However, some patients become resistant to treatment and require surgery [1, 2].

Total parathyroidectomy with autotransplantation in brachioradialis muscle has been recommended because in cases of hyperparathyroidism recurrence, the approach in forearm is, technically, more simple and can be performed with locoregional anesthesia, whereas the cervical approach has higher morbidity. Moreover, it allows the

assessment of the grafted tissue using a comparative PTH measurement between the superior members [3–7].

PTH secretion capacity from the autotransplanted gland has been demonstrated through the blood measurement in basal conditions [8]. Dynamic tests have been used to analyze the behavior of parathyroid glands in primary and secondary hyperparathyroidism [9, 10]. However, few studies clarify the function of parathyroid tissue after transplantation into muscle [11–13]. Thus, this study was designed to determine the suppression ability and secretion reserve of PTH in induced hypercalcemia and hypocalcemia status, respectively, in patients who underwent parathyroidectomy and partial autotransplantation into brachioradialis muscle.

Materials and methods

Twelve patients [8 women and 4 men; age, 38.8 ± 10.6 (mean ± SD) years], with the diagnosis of secondary hyperparathyroidism to chronic renal failure, on hemodialysis for more than 4 years (8.6 ± 2.8 years), from an Outcome Clinic for Renal Osteodystrophy, in Clinical Hospital of Ribeirão Preto Medical School, University of São Paulo, were referred to the Head and Neck Surgery Unit from the same hospital for surgical treatment between February 1, 2003 and January 30, 2005.

Patients had serum levels of PTH; phosphorus and alkaline phosphatase increased. All patients had evidence of severe secondary hyperparathyroidism with PTH serum levels >500 pg/ml. The serum PTH levels ranged from 1,373 to >2,500 pg/ml (2,238 ± 419 pg/ml; reference range, 10–69 pg/ml), inorganic phosphorus ranged from 4 to 6.8 mg/dl (5.8 ± 1 mg/dl; reference range, 2.5–5.6 mg/dl), and phosphatase alkaline ranged from 520 to 2,114 U/L (1,418 ± 487 U/L; reference range, 65–300 U/L). The mean serum levels of ionized calcium was 1.20 ± 0.1 mmol/l (reference range, 1.12–1.32 mmol/l). No patient had alteration of liver function, and all had serum levels of alanine aminotransferase, aspartate aminotransferase, and gama-glutamil transferase in the normal range. The parathyroid scintigraphy was performed before surgery to show the location of the parathyroid glands. Patients older than aged 65 years and younger than aged 18 years were excluded, as well patients with bone disease due to other etiologies. The osteitis fibrosa cystica was confirmed by biopsy, followed by bone histomorphometry.

All procedures were made by the same surgeon. The surgery was performed under general anesthesia and orotracheal intubation. A Kocher incision was used to neck exploration. All four glands were identified and removed. After frozen-section confirmation, an autotransplantation to brachioradialis muscle of 16 fragments of 1 mm^3 parathyroid tissue was performed. Intravenous gluconate calcium was administered after the last parathyroid removal to prevent severe hypocalcemia. All patients were discharged using oral calcium and calcitriol. The postoperative serum PTH measurement was performed immediately before the dynamic tests.

For functional assessment of grafted parathyroid glands, two dynamic tests of PTH secretion were used to stimulate and suppress the parathyroid gland secretion. The experiments began between 8 and 9 o'clock in the morning and were conducted with the patient in the supine position in a metabolic study room at a constant temperature of 22°C. Cubital veins were cannulated in each forearm with 20-gauge butterfly catheters for solution infusion and blood collection. The solution was infused with an infusion pump (Harvard Apparatus) into the contralateral arm to that used for blood collection. Blood samples were collected from the non-grafted arm. Both tests were performed during the late postoperative period (LP): 345 (SD = 38) days after surgery. Additional stimulation tests were performed during the recent postoperative period (RP): 165 (SD = 16) days after surgery.

Hypercalcemic suppression

The samples were collected at 10-min intervals during the basal period and first hour, and at 20-min intervals in the second hour during the 2-h period of calcium infusion. A solution of calcium gluconate 10% (2.5 mg/kg) was prepared, diluted in 5% glucose solution to a total volume of 100 ml. The test was performed in LP.

Hypocalcemic stimulation

Blood samples were collected at 10-min intervals during the basal period (30 min) and during a 2-h period of ethylenediaminetetraacetic acid (EDTA) infusion. The solution was prepared immediately before administration containing EDTA (30 mg/kg) (Pharmacy—HCFMRP/USP), lidocaine 2% (2.7 mg/kg) (Astra Zeneca), and 5% glucose for a total volume of 200 ml. The tests were done in RP and LP.

Blood samples for the determination of intact PTH was centrifuged and serum samples were frozen at −70°C for later PTH determination. PTH was determined in serum by the immunochemiluminometric assay (Diagnostic Products Corporation, Los Angeles, CA), with lower limit of detection of 1 pg/ml. The intra-assay variation was 1.2–3.7% and interassay of 8.1%. The ionized calcium was determined immediately after collection to detect risk of hypocalcemia or hypercalcemia. It was determined in an analyzer with

calcium-specific electrode (Radiometer, Copenhagen, Denmark).

The tests were performed with an interval of at least a week. Ten patients were evaluated in both suppression and stimulation tests. One patient did not participate in the stimulation test in RP (patient 12) and other one in LP (patient 5; Table 1). Fourteen volunteers formed the control group. All were healthy and they did not use medications that may interfere with calcium metabolism or PTH secretion, such as calcium and vitamin D. Each individual was tested for stimulation of the parathyroid gland with EDTA and suppression with calcium infusion, applying the same methods. The study was approved by the Ethics Committee in Research of the HCFMRP-USP, and patients and individuals in the control group were informed about the procedures that they would be undergo before they signed informed consent.

Statistical analysis was performed using the linear mixed-effect model, with logarithm in time variable for method adequacy. Data were analyzed using a Bayesian approach, comparing the slope coefficient of ionized calcium and PTH curves. The application of the statistics methods was performed using the Winbugs and R software, with significance set as 5% ($p < 0.05$).

Results

In RP, there was a decrease in the average serum levels of PTH, phosphorus, and alkaline phosphatase, which ranged from 13 to 231 (87 ± 65) pg/ml, 2.3 to 6.2 (3.3 ± 1.1) mg/dl, and 77 to 504 (250 ± 135) U/L, respectively. In LP, there was slight variation in laboratory parameters compared with RP (Table 1).

Hypercalcemic suppression

Infusion of 10% calcium gluconate increased the serum calcium level in 12% in relation to baseline value of the uremic patients. In the control group, there was an increase of 16%. Nevertheless, the curve of the ionized calcium serum levels showed similar slope coefficient in patients and the control group ($p > 0.05$). At the same time, in patients, the average concentration of serum PTH at baseline was 114 ± 121 pg/ml, and at the time of 10 min during the test, it was 76 ± 92 pg/ml ($\Delta = 38$ pg/ml), representing decrease of 33%. In the control group, there was a decrease of 26 ± 14 pg/ml to 2.0 ± 2.6 pg/ml in 100 min during the test, representing a decrease of 92%. Therefore, there was no significant decrease in the PTH levels of the patients when analyzing the curve slope coefficient concerning PTH secretion (Fig. 1).

Hypocalcemic stimulation

In the first evaluation (RP), there was a decrease of 11% in the average levels of calcium ($\Delta = 0.1$ mmol/l), whereas in the second evaluation (LP) there was a decrease of 12% ($\Delta = 0.12$ mmol/l). The statistical comparison between the slope coefficients of the calcium curve in these tests did not show statistical differences compared with control group calcium curve. Serum PTH levels during the test did not

Table 1 Changes in parathyroid hormone, ionized calcium, phosphorus, and alkaline phosphatase serum levels in control subjects, preoperative, recent postoperative, and late postoperative periods

Patients (Preop/RP/LP)	PTH (pg/ml)	Ionized calcium (mmol/l)	Phosphurus (mg/dl)	Alkaline phosphatase (U/L)
1	>2,500/135/236	1.1/0.8/1	4.8/4.3/2.9	898/257/151
2	2,365/125/47	1/0.9/1.2	6.8/3.8/3.1	1,300/266/257
3	2,132/33/47	1.2/0.7/1.2	6.1/2.8/3.4	1,928/197/178
4	>2,500/58/52	1.2/0.9/0.7	6.6/2.8/5.7	1,029/138/133
5	1,389/53/ne	1.4/0.8/ne	6.1/2.4/ne	520/136/ne
6	2,466/32/23	1.1/0.9/1.2	5.9/3.5/2.7	1,092/150/112
7	2,432/131/58	1.2/1.1/1	6.8/6.2/6.4	1,626/77/67
8	>2,500/42/50	1/1.2/1.1	5/2.3/2.9	2,114/305/135
9	1,373/231/245	1.2/0.8/0.8	4.5/3.6/4.1	1,664/504/412
10	2,197/101/68	1.3/1.1/1.1	4/2.5/3.8	1,220/251/266
11	>2,500/13/131	1.2/1.2/1.2	6.3/2.6/4	1,630/467/110
12	>2,500/ne/194	1.2/ne/0.7	6.7/ne/4.3	1,995/ne/445
Mean	2,238/87/105	1.2/0.9/1.0	5.8/3.3/3.9	1,418/250/206
SD	419/65/83	0.1/0.2/0.2	1.0/1.1/1.2	487/135/125

PTH parathyroid hormone, *Preop* preoperative, *RP* recent postoperative, *LP* late postoperative

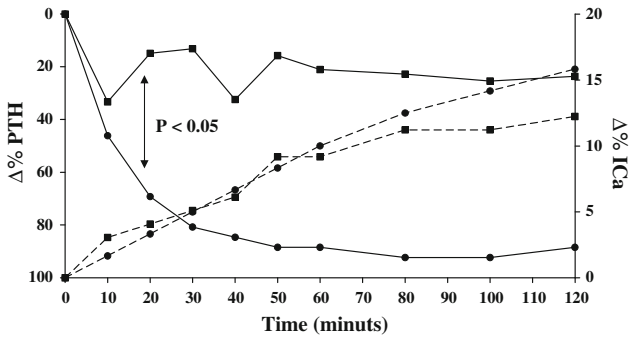

Fig. 1 (- -) Mean ionized calcium (ICa) and (–) parathyroid hormone (PTH) serum variation (Δ%) in hypercalcemic suppression test in control subjects (●) and patients during late postoperative (LP) period (■)

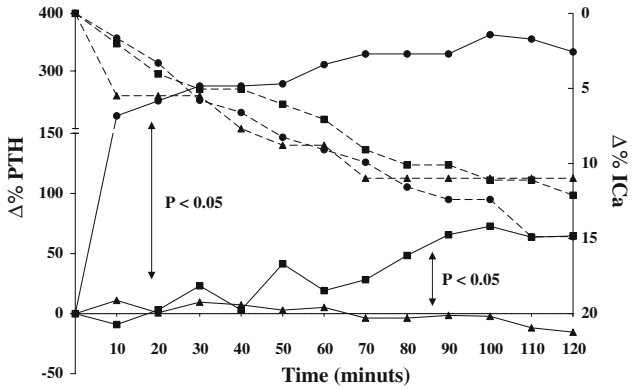

Fig. 2 (- -) Mean ionized calcium (ICa) and (–) parathyroid hormone (PTH) serum variation (Δ%) in hypocalcemic stimulation test in control individuals (●) and patients during recent postoperative (RP) period (▲) and late postoperative (LP) period (■)

show a significant variation in RP, whereas in LP there was a greater response. The increase in serum PTH (pg/ml) levels in the control (27 ± 15 to 125 ± 62), RP (136 ± 123 to 151 ± 142), and LP (99 ± 103 to 172 ± 137) groups was 363% (100 min), 11% (10 min), and 73% (100 min), respectively. The analysis of the PTH curves showed significant differences between the two evaluations (RP and LP) in patients and the control group (Fig. 2).

Discussion

The hyperparathyroidism status is a serious complication in uremic patients. Although dialysis treatment has emerged as the effective way for life maintenance in patients with renal failure, it was noted later that most patients had a chronic hypersecretory response from parathyroid glands, often with serious consequences, debilitating, and compromising the quality of life [14].

In this study, the successful outcome of surgery could be confirmed by measuring the serum PTH during the postoperative period. It was observed that, recently after surgery, the reduction of serum PTH concentrations was near 95% less than values before surgery.

During the stimulation test of PTH secretion using EDTA, we observed significant decrease in ionized serum calcium levels in studied patients, both in recent and in late postoperative period. Because there was no difference between groups, we considered the test was effective and was possible to compare the groups concerning the PTH secretory response, because the stimuli, represented by the variation in ionic calcium levels, were equivalent. Despite the similar hypocalcemic stimulation, the groups had different responses on the PTH secretion. The slight secretory response observed in patients evaluated in RP shows that, so far, the patients who underwent total parathyroidectomy with autotransplantation have minimal secretory capacity in response to hypocalcemia. This suggests that these patients have less secretory reserve compared with healthy individuals. In LP, the curve of PTH secretion presented intermediate values compared with those observed in the control group and patients in RP. This behavior can mean a partial recovery of the ability of PTH secretion toward normality, represented in this study by the curve of the individuals in the control group.

Studies in dynamics of PTH secretion performed before parathyroidectomy present findings similar to those observed in this study [15]. Ramirez et al. (1993) evaluated 13 patients with secondary hyperparathyroidism using test of hypocalcemia induction by infusion of citrate and observed an average increase of 396% of serum PTH level in health individuals, whereas in the patients there was an increase of 79%, suggesting a reduced capacity to secrete PTH [16]. The same was observed in this study, where the increase of PTH was 363% in the control group, and in the LP assessment patients increased the PTH secretion in 73%. This impairment in the secretory response can mean that a glandular change, before surgery, may be responsible for the low capacity of secretion in patients undergoing total parathyroidectomy with autotransplantation. Glandular intrinsic abnormalities have been demonstrated in hyperparathyroidism, such as somatic mutations in the calcium receptor, decrease in receptors quantity on this tissue, reduction on the sensitivity of receptors, and changes in the mechanisms of receptor signaling, may contribute to induce abnormalities of secretory response to calcium variation [17–22].

The gland behavior analysis in the suppression test demonstrated an inability to reduce the PTH secretion, despite the satisfactory levels of hypercalcemia reached. The average curve of PTH secretion did not demonstrate a significant change during the test. This observation is

consistent with the study by De Castro et al. (1999), which analyzed the ability of PTH secretion through hypo- and hypercalcemia, induced during hemodialysis, observing subnormal ability of blocking the PTH secretion in a patient, 15 days after parathyroid autotransplantation [11].

Conclusions

Total parathyroidectomy followed by partial autotransplantation was effective in reducing PTH serum levels in patients with terminal kidney disease. The elevation of serum calcium during the suppression test was not able to inhibit the autograft gland secretion of PTH. The assessment of parathyroid graft function demonstrated an inability to respond to the stimulus of hypocalcemia induced by EDTA, although there was a partial recovery, in late postoperative period.

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