Parathyroid responsiveness during hypocalcemia after total parathyroidectomy and autotransplantation in patients with renal hyperparathyroidism

Responsividade paratireoideana à hipocalcemia após paratireoidectomia total com autoimplante em portadores de hiperparatireoidismo associado à doença renal crônica

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ABSTRACT

Introduction: Hyperparathyroidism is a frequent complication of chronic kidney disease (CKD). Total parathyroidectomy (PTX) with parathyroid tissue autotransplantation (AT) is a treatment option in those individuals that do not respond to clinical management. **Objective:** To evaluate grafted parathyroid tissue response during induced hypocalcemia among CKD patients who underwent total PTX with AT. **Methods:** Eighteen patients with renal hyperparathyroidism were submitted to total PTX with parathyroid AT selected by stereomicroscopy between April and October 2008. Eleven (eight with successful kidney transplantation, 2 in peritoneal dialysis and 1 in hemodialysis) were clinically stable and eligible for testing. Hypocalcemia was induced using sodium bicarbonate infusion in 5 healthy controls and in patients 6-12 months after surgery. **Results:** Among controls, hypocalcemia elicited a major rise in intact PTH (iPTH) levels 4 minutes after bicarbonate infusion. In patients, a significant decrease in ionized calcium concentration was observed [from 1.17 ± 0.12 to 1.09 ± 0.11 mean (± SE) mmol/L] in the 4th minute ($p < 0.001$) illustrating the nadir point. In the 10th minute, ionized calcium did not show a statistical increase compared to the 4th minute ($p = 0.451$). The iPTH levels ranged from 34.8 ± 18.6 to 34.1 ± 18.8 pg/mL (similar values between base line and 4th minute $p = 0.087$) and did not change in the 10th minute (33.3 ± 19,6 pg/mL $p = 0.693$). **Conclusion:** Among CKD patients tested 6-12 months after surgery, grafted parathyroid tissue revealed a blunted secretory capacity during bicarbonate induced hypocalcemia with no changes in iPTH levels

Keywords: hyperparathyroidism; hypocalcemia; parathyroid hormone; parathyroidectomy; renal insufficiency, chronic.

RESUMO

Introdução: O hiperparatireoidismo é uma complicação frequente da doença renal crônica (DRC). A paratireoidectomia (PTX) total com autotransplante (AT) de tecido paratireoideano é uma opção terapêutica para os indivíduos que não respondem ao manejo clínico. **Objetivo:** Avaliar a resposta do tecido paratireoideano enxertado durante hipocalcemia induzida em pacientes portadores de DRC submetidos à PTX total com AT. **Métodos:** Dezoito pacientes portadores de hiperparatiroidismo associado à DRC foram submetidos à PTX total com AT de tecido paratireoideano selecionado por estereomicroscopia entre Abril e Outubro de 2008 em nosso serviço. Onze indivíduos (oito com transplante renal funcionante, 2 em diálise peritoneal e 1 em hemodiálise) apresentavam boa condição clínica e foram elegíveis para o teste. Induziu-se hipocalcemia por infusão de bicarbonato de sódio em 5 controles normais e nos pacientes 6-12 meses após a PTX. **Resultados:** A hipocalcemia determinou um aumento importante dos níveis de PTH intacto (iPTH) no grupo controle 4 minutos após a infusão de bicarbonato. Nos pacientes, houve uma redução significativa do cálcio ionizado [de 1,17 ± 0,12 para 1,09 ± 0,11 (media ± EP) mmol/L] no 4º minuto ($p < 0,001$) ilustrando o nadir do teste. No 10º minuto não houve elevação do cálcio ionizado comparado ao 4º minuto ($p = 0,451$). Os níveis de iPTH foram de 34,8 ± 18,6 para 34,1 ± 18,8 pg/mL (valor basal semelhante ao 4º minuto $p = 0,087$) e se mantiveram no 10º minuto (33,3 ± 19,6 pg/mL $p = 0,693$). **Conclusão:** Em pacientes portadores de DRC testados 6-12 meses depois da cirurgia, o enxerto de tecido paratireoideano revelou incapacidade de resposta à hipocalcemia induzida por bicarbonato sem mudança dos níveis de iPTH.

Palavras-chave: hiperparatireoidismo; hipocalcemia; hormônio paratireóideo; insuficiência renal crônica; paratireoidectomia.

Introduction

Hyperparathyroidism is a frequent and severe complication of chronic kidney disease (CKD). Despite advances in medical therapy, treatment failure still occurs in a significant number of patients in which parathyroidectomy (PTX) is indicated.[1] Surgical technique options are subtotal PTX and total PTX with or without parathyroid tissue autotransplantation (AT).[2] The best surgical approach is yet to be defined. Controversy remains since neither high postsurgical recurrence rates nor the presence of definitive hypoparathyroidism are intended. If total PTX with autotransplantation (AT) is to be chosen, close examination of glands during the procedure is essential to graft´s selection. To do so, one can use a stereomicroscope intraoperatively to differentiate parathyroid normotropic areas by the presence of stromal fat cells from those that are dysfunctional and hyperplastic.[3] Parathyroid tissue can also be cryopreserved after selection for further reimplant in those subjects who develop permanent hypoparathyroidism.[4,5]

However, the viability of stored tissue reduces with prolonged cryopreservation time.[6] Therefore, evaluation of graft´s secretory reserve through a physiologic stimulus could be an interesting approach in trying to predict which patient could benefit from reimplant considering that shorter periods may improve cryopreserved tissue functionality. Acute hypocalcemia is the major trigger of PTH release in normal subjects.[7]

The Ethylenediamine tetraacetic acid (EDTA) infusion test has been previously used to induce hypocalcemia and stimulate PTH release[8] but is not widely employed because it is time-consuming and has potential adverse cardiovascular effects. Iwasaki *et al.* have proposed the use of sodium bicarbonate (BIC) infusion test to induce hypocalcemia and evaluate parathyroid secretory reserve in several diseases.[9] The rational of the test in that the acute infusion of BIC leads to a transient rise in blood pH followed by a decrease in ionized calcium concentration which, in turn, stimulates PTH release. Few studies have demonstrated the functional response of parathyroid tissue after total PTX with AT during induced hypocalcemia.[10-13]

The aim of this study was to assess graft´s PTH secretory response during induced hypocalcemia in patients with renal hyperparathyroidism who underwent total PTX with AT selected by stereomicroscopy.

Methods

This was an experimental study on a group of patients treated at the Federal University of São Paulo Medical School (UNIFESP/EPM) in São Paulo, Brazil. The study was conducted in accordance with the principles of the Declaration of Helsinki/Guidelines on Good Clinical Practice and was approved by the institution´s ethical committee (approval No. CEP 0354/09).

Control group

Five healthy individuals (18 years or older of any gender) living in São Paulo, Brazil volunteered to be studied during induced hypocalcemia. None of them used medication that may interfere with calcium metabolism or PTH secretion. Controls were tested before patients to confirm procedure's safety and to adjust protocol, if necessary. Signed informed consent was also obtained and there was no benefit of participating in this research.

Patient group

Patients were followed at the Bone Disease Unit because of renal hyperparathyroidism. They were referred to the Head and Neck Surgery Unit from the same hospital for surgical treatment if there was persistent hypercalcemia not responsive to medical interventions and/or persistent hyperphosphatemia despite clinical management associated with signs and symptoms such as intractable pruritus, severe bone pain, fractures or high risk of fracture, skeletal deformities, extra-skeletal calcifications and/or development of calciphylaxis.

Surgical procedure

Eighteen patients underwent total PTX with AT to treat severe renal hyperparathyroidism between April and October 2008. All of them had at least four parathyroid gland excision checked by frozen section examination and/or intraoperative PTH measurements to confirm surgical cure. Removed parathyroid glands were carefully examined by stereomicroscopy (using a Leica Stereo Zoom S8 APO Stereomicroscope with magnification of 10-80x, Leica Mycrosystems GmbH- Wetzlar, Germany)

to select an non-nodular area rich in stromal fat cells for immediate graft implant.

The site chosen for autotransplantation was the presternal musculature over a single area of 1,5 cm in length over the upper one-third of the sternum. Around 30 parathyroid fragments sized 2 mm^3 each were implanted. Another 30 parathyroid fragments were frozen at -70°C (cryopreservation) in a solution containing 60% of RPMI or DMEM, 30% of fetal bovine serum and 30% of DMSO (dimetilsulfoxide) for further reimplant, if needed. All procedures were made by the same surgeon.

Patient selection

The inclusion criteria for functional assessment of grafted parathyroid glands were: (a) any gender and age of 18 years or older (b) having total PTX with AT by the technique an within the period mentioned above (c) time between study test and PTX should range from 6 to 12 months and (d) the acceptance to participate to the study (signed informed consent form). Exclusion criteria were the presence of hypocalcemia in the last medical evaluation performed between 10 to 40 days before the test and the presence of any medical condition that required hospitalization.

Study protocol: hypocalcemic stimulation

All individuals were advised to consume their normal diet and remain in fasting conditions for at least 4 hours before the study test. All medication, if there was any, was maintained with the exception of calcitriol and calcium carbonate that were suspended on test day and taken after the procedure. If patient was in hemodialysis, the test was performed the day after a regular dialysis session. If they were in peritoneal dialysis, the test was made before changing the first solution of the day. The experiment began between 8:00 and 9:00 AM with subjects in a sitting position in room temperature.

The test was performed as follows: base line blood samples were obtained from a peripheral arm vein cannulated with a 20-gauge butterfly catheter. Tourniquet was used only for catheter insertion and then removed. Subsequently, 35 mL per Body Surface Area (BSA in m^2) of a 8.4% Sodium Bicarbonate (BIC) solution was injected into a peripheral vein of the other arm during 2 minutes. BSA was calculated by the equation: BSA (m^2) = 0.20247 x Height(m)$^{0.725}$ x Weight(kg)$^{0.425}$ (the DuBois Formula).

Blood samples from the base line venipuncture were collected again at 4 and 10 minutes following the start of BIC infusion. Samples for determining ionized plasma calcium, pH and bicarbonate ion concentration were collected using heparinized 1 mL syringes for immediate measurements. Blood samples to be used in the analysis of plasma intact PTH (iPTH) concentrations were collected using tubes containing EDTA, centrifuged right after the end of the test and kept frozen at -20°C for subsequent analysis. A meal rich in calcium was offered to every subject (half cup of milk, 50 g of cheese and 120 mL of yogurt) and they were under our observation for at least 30 minutes after eating and before their release.

Biochemical analyses

Ionized plasma calcium was measured using an ion-specific electrode (AVL 9180 Eletrolyte Analyzer USA) with a reference value of 1,12-1,32 mmol/L. Intact PTH was measured using Elecsys PTH immunoassay (Elecsys 1010 System, Roche, Mannheim, Germany) with a reference value of 15-65 pg/mL. Blood bicarbonate (reference 23-27 mmol/L) and pH (reference 7.33-7.43) were measured using standard automatic assays.

Statistical analysis

Data were summarized as mean and standard error (SE). Repeated measures two-way ANOVA models were performed to analyze differences between-groups and within-groups. Pearson´s correlation, Fischer´s exact test and *T*-Sudent test were used to account for baseline differences between groups. A *p*-value of < 0.05 was considered significant.

Results

Five controls (two men, three women) were studied and had average age of 31.2 (range 26 to 39) years. BSA and BIC infusion volume mean values were 1.70 m^2 and 59.4 mL, respectively. Venous blood gas test results were available in three of the five controls (two had analysis problems) while ionized calcium and iPTH measurements were available in all five individuals. The mean (± SE) blood pH (7.41 ± 0.02) was found to be significantly increased following the BIC injection (7.46 ± 0.03) in the 4th minute ($p < 0.001$) and in the 10th minute (7.45 ± 0.02, $p = 0.035$).

Blood bicarbonate concentration did not show significant elevation in this group from baseline to

4th minute (27.00 ± 2.00 to 29.33 ± 1.15 mmol/L, p = 0.349) and to 10th minute (29.67 ± 0.58 mmol/L, p = 0.134). A significant decrease in ionized calcium concentration was observed (from 1.23 ± 0.05 to 1.08 ± 0.20 mmol/L) in the 4th minute (p = 0.008) which characterized the nadir point (mean reduction of 12.1% from the baseline ionized calcium).

Afterwards, ionized calcium increased reaching levels similar to base line values (p = 0.180) in the 10th minute (1.21 ± 0.03). In response to the decrease in ionized calcium, a prompt and marked rise in iPTH levels (from 38.1 ± 10.7 to 116.4 ± 33.9 pg/mL) was observed in the 4th minute sample (p < 0.001) followed by a decrease in the 10th minute (64.2 ± 29.3 pg/mL) that was still significantly higher than base line levels (p < 0.001).

In patient group, 11 of the 18 patients submitted to total PTX with AT between April and October 2008 were selected for testing. The remainders did not meet clinical criteria or did not consent. Among 11 patients (eight women, three men), the mean age was 47.9 (range, 40-62) years and eight of them (73%) had renal transplantation (all of which were transplanted before PTX and had functioning grafts for an average of 4.3 years).

At the time of the test, their average serum creatinine was of 1.23 mg/dL. The period of dialysis before transplant was in average 5.4 years. The remaining three patients (27%) were currently in dialysis treatment: two in CAPD (Continuous Ambulatory Peritoneal Dialysis) and one in hemodialysis for an avarege of 5.3 years. The Ca^{++} concentration in both peritoneal and hemodialysis solution was of 3.5 mEq/L.

The etiology of CKD was unknown in all of the 11 patients (classified as chronic glomerulonephritis). Calcitriol 0.25 mcg and calcium carbonate ($CaCO_3$) 500 mg were being used by 64% of the patients (range, 0.5 to 2 pills a day for calcitriol and range, 1 to 2 pills a day for $CaCO_3$). Study tests were done between January and July 2009 and mean time between surgery and testing was of 8.8 months (range 6 to 12). A summary of patient´s data is presented in Table 1.

BSA and BIC infusion volume mean values were similar to controls (1.70 m^2; 59.6 mL, respectively). In patient group, the blood pH (7.35 ± 0.03) increased significantly after BIC injection (7.46 ± 0.05) in the 4th minute (p < 0.001) and in the 10th minute (7.42 ± 0,03, p < 0.001). Blood bicarbonate concentration showed significant elevation in this group from baseline to 4th minute (26.06 ± 3.2 to 31.24 ± 5.8 mmol/L, p = 0.003) and to the 10th minute (28.8 ± 4.39 mmol/L, p = 0,009).

A significant decrease in ionized calcium concentration was observed (from 1.17 ± 0.12 to 1.09 ± 0.11nmol/L) in the 4th minute (p < 0.001) illustrating the nadir point (mean reduction of 6.8% from the baseline ionized calcium). In the 10th minute, ionized calcium did not show a statistical increase compared to the 4th minute (p = 0.451) and remained lower than base line values (p = 0.027). Plasma iPTH did not rise in response to decreased ionized calcium: levels ranged from 34.8 ± 18.6 to 34.1 ± 18.8 pg/mL (base line x 4th minute, p = 0.087) and maintained similar values in the 10th minute (33.3 ± 19.6 pg/Ml, p = 0.693).

Figure 1 illustrates ionized calcium and iPTH responses to the test in both groups. Additionally, there was no difference between transplanted and dialytic patients concerning degree of PTH response during induced hypocalcemia.

Comparison between controls and patients

Baseline pH was higher in the control group (p = 0.034) but was not different after BIC injection in the 4th (p = 0.842) or 10th (p = 0.332) minutes between groups. Blood bicarbonate values were similar between controls and PTX patients in all measurements (Baseline: 27.00 ± 2.00 to 26.06 ± 3.2 mmol/L, p = 0.521; 4th minute: 29.33 ± 1.15 to 31.24 ± 5.8 mmol/L, p = 0.595; 10th minute: 29.67 ± 0.58 to 28.81 ± 4.39 mmol/L, p = 0.751).

Ionized calcium showed no difference between groups in base line and 4th minute. The ionized calcium in the 10th minute in the PTX group tended to be lower but did not reach statistical significance. Plasma PTH was similar at base line between groups and significantly higher in the 4th minute and still higher in the 10th minute in the control group (Table 2).

Side effects

Although side effects were common, they were mild and well tolerated. Coldness sensation in the injected arm throughout BIC infusion was referred by 3/5 of the controls (60%) and 5/11 of the patients (45.5%). Oral paresthesia was reported in one subject of the patient group in the 4th minute and dizziness occurred

Table 1 Patient´s base line characteristics

Patients	Sex	Tx	PTX (mo/yr)	Test (mo/yr)	Calcitriol (0.25 mcg)	$CaCO_3$ (500 mg)	iCa (mmol/L)	iPTH (pg/mL)
1	F	Yes	04.2008	01.2009	2	2	1.09	15.2
2	F	No*	05.2008	02.2009	1	2	1.26	8.2
3	M	Yes	05.2008	02.2009	0	0	1.15	45.3
4	F	Yes	05.2008	02.2009	1	2	1.31	49.0
5	M	Yes	06.2008	02.2009	2	1	1.04	28.3
6	F	Yes	07.2008	03.2009	0.5	0	1.03	27.0
7	F	Yes	06.2008	03.2009	0	1	1.11	16.7
8	F	No*	10.2008	05.2009	0	0	1.25	58.4
9	F	Yes	08.2008	06.2009	0	0	1.13	59.9
10	M	Yes	06.2008	06.2009	2	2	1.13	52.1
11	F	No*	09.2008	07.2009	2	2	1.39	22.7
Patients	Sex	Tx	PTX (mo/yr)	Test (mo/yr)	Calcitriol (0.25 mcg)	$CaCO_3$ (500 mg)	iCa (mmol/L)	iPTH (pg/mL)
1	F	Yes	04.2008	01.2009	2	2	1.09	15.2
2	F	No*	05.2008	02.2009	1	2	1.26	8.2
3	M	Yes	05.2008	02.2009	0	0	1.15	45.3
4	F	Yes	05.2008	02.2009	1	2	1.31	49.0
5	M	Yes	06.2008	02.2009	2	1	1.04	28.3
6	F	Yes	07.2008	03.2009	0.5	0	1.03	27.0
7	F	Yes	06.2008	03.2009	0	1	1.11	16.7
8	F	No*	10.2008	05.2009	0	0	1.25	58.4
9	F	Yes	08.2008	06.2009	0	0	1.13	59.9
10	M	Yes	06.2008	06.2009	2	2	1.13	52.1
11	F	No*	09.2008	07.2009	2	2	1.39	22.7

F: Female; M: Male; Tx: Transplant; PTX: parathyroidectomy; $CaCO_3$: calcium carbonate; iCa: ionized calcium; PTH: intact parathyroid hormone; * Patient 8 was in hemodialysis and patients 2 and 11 were in CAPD (continuous ambulatory peritoneal dialysis).

in one subject of the control group in the 10th minute. All symptoms resolved spontaneously in less than one minute.

Discussion

Severe renal hyperparathyroidism is a relatively common clinical presentation in our country. According to the Brazilian Census of Parathyroidectomy, the prevalence rate of severe hyperparathyroidism (iPTH > 1.000 pg/mL) in dialysis patients was of 10.7%, a situation in which PTX is practically unequivocal.[14] To a lesser extent, the prevalence of renal transplanted patients in which PTX is required is around 3.1% in a local study.[15] The management of these cases represents a real challenge.[16]

The 2009 KDIGO guidelines suggest PTX in CKD patients who fail to respond to medical therapy. PTX performed by an expert surgeon generally results in a sustained reduction in levels of serum PTH, calcium, and phosphorus. Subtotal PTX or total PTX with autotransplantation are possibilities and there is no evidence of superiority between either techniques.[17] The approach chosen by our group was total PTX with presternal intramuscular AT.

Among 66 patients with severe renal hyperparathyroidism operated in our center, graft-dependent recurrence occurred in six individuals (9.0%) and definitive hypoparathyroidism was observed in four (6.0%) within the 1st and 5th year after surgery demonstrating the feasibility and safety of this technique.[18] Magnabosco *et al.*[19] compared the indications and results of different surgical strategies in severe renal hyperparathyroidism through a systematic literature review from January 2008 to March 2014. The ideal technique should provide low recurrences rates, low risk of permanent hypoparathyroidism and easy access to the gland during recurrence treatment. From the 49 articles selected, 47,0% preferred total

Figure 1. (Square) mean ionized calcium (iCa) and (Dot) mean parathyroid hormone (iPTH) serum variation through time (Baseline, 4 and 10 minutes) in patients and controls. Normal range in gray (iCa 1.12-1.32 mmol/L and iPTH 15-65 pg/mL).

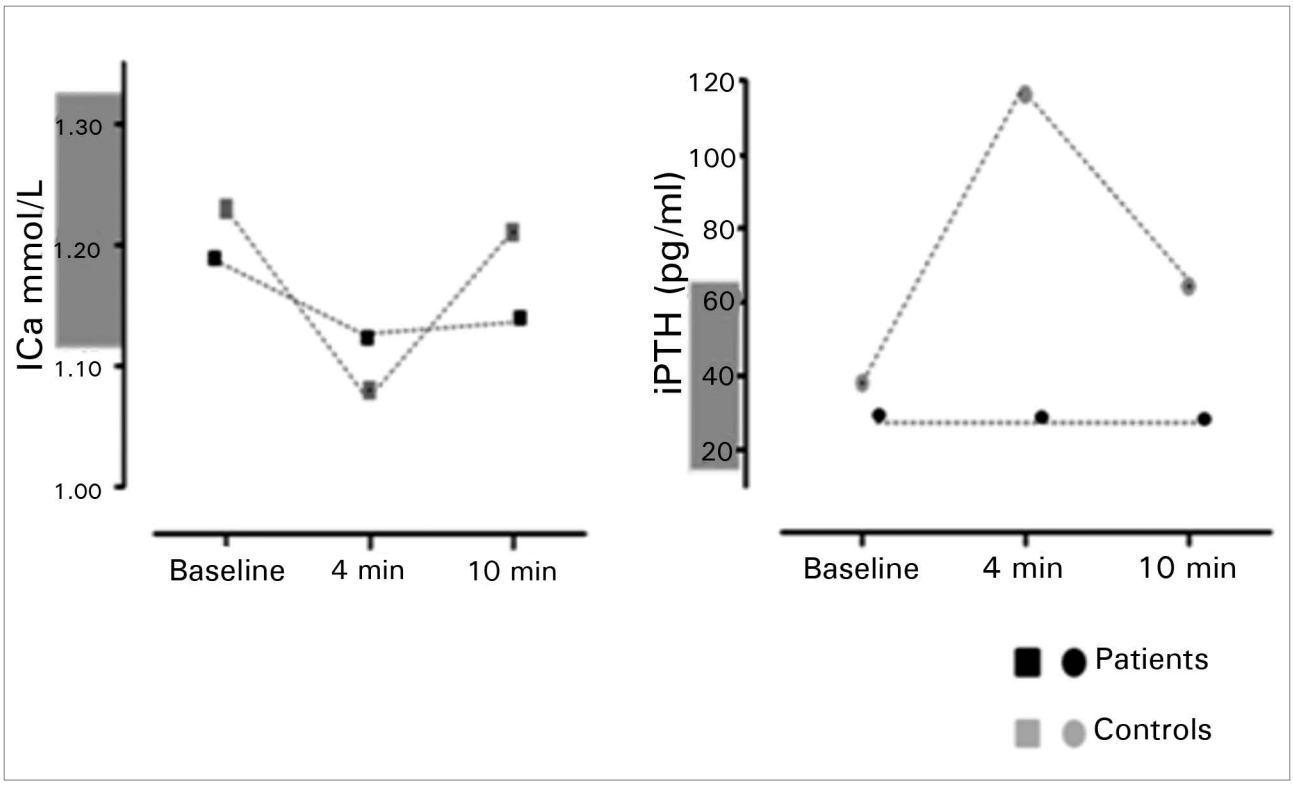

Table 2 Comparison between ionized calcium (iCa) and parathyroid hormone (PTH) through time

	Groups		
	Patients (n = 11) Mean value (SE)	Controls (n = 5) Mean value (SE)	*p*-value
iCa (1.12-1.32 mmol/L)			
Base line	1.17 (0.12)	1.23 (0.05)	0.275
4 min	1.09 (0.11)	1.08 (0.20)	0.916
10 min	1.11 (0.11)	1.21 (0.03)	0.064
iPTH (15-65 pg/mL)			
Base line	34.8 (18.62)	38.1 (10.71)	0.717
4 min	34.1 (18.83)	116.4 (33.91)	< 0.001
10 min	33.3 (19.64)	64.2 (29.31)	0.025

PTX with AT, followed by subtotal PTX and only a minority of studies chose total PTX.

Conzo *et al.*[20] evaluated 40 dialytic patients with severe hyperparathyroidism eligible for renal transplantation that underwent Total PTX and AT. For these patients, the author suggests that subtotal PTX or Total PTX with AT should be the techniques of choice. Conversely, total PTX without AT should be reserved for those with no perspective of renal transplantation which have longer dialysis time and more aggressive hyperparathyroidism.

Tissue selection for autotransplantation is challenging. The criterion based on macroscopic observation is the routine procedure in most centers. In our study, we used stereomicroscopy in attempt to improve parathyroid tissue selection for AT.[21] The stereomicroscope can selected normotropic areas rich in stromal fat cells which maintain the ability of PTH suppression in the presence of high calcium levels *in vitro*.[22]

During the stimulation test, we observed a significant decrease in ionized serum calcium levels in

both groups throughout BIC infusion. However, only healthy controls exhibited a marked rise iPTH levels while all of the 11 patients did not respond. There are some factors that could explain this finding. Glandular changes before surgery are related to abnormalities in secretory response to serum calcium variations that include lower vitamin D receptor density in the adenomatous cells, reduced expression of the extracellular calcium-sensing receptor, sensitivity and signaling.[23-25] Noteworthy, renal transplantation does not seem to affect the iCa response range or the sensitivity of the parathyroid gland to changes in iCa one year after transplantation.[26]

In our patients the time between surgery and study test was of 8,8 months (range 6 to 12) and the site chosen to autotransplantation was the presternal musculature. Heterotopic transplantation and the period chosen to perform the test may have influenced our results: Parathyroid glands are densely innervated by sympathetic, parasympathetic and sensory nerve fibers.[27]

Schmitt *et al.*[12] have investigated the effect of total PTX with AT on PTH secretion patterns in nine patients with end-stage renal disease in early (1 to 8 weeks) and late (15 to 33 months) phase after surgery. Spontaneous PTH secretion was observed in all patients and citrate and calcium clamp studies were performed late after PTX in 4 patients. They observed that physiologic pulsatile mode of PTH release is profoundly disturbed during the first 2 months after surgery but it recovers partially in patients studied at least 15 months after the procedure.

This suggests that autonomic reinnervation graft contributes to eventual coordinate pulsatile secretion. On the other hand, the capacity to modulate PTH release in response to changes in iCa during clamp studies remained markedly reduced in late period indicating that functional reinnervation may not correct abnormal calcium sensing.[12]

Conti-Freitas *et al.*[13] studied the dynamics of PTH release in early (5,5 months) and late (11,5 months) period after total PTX with AT using EDTA infusion test to induce hypocalcacemia. They observed a lack of PTH secretion in the early period and partial response in the late period which can mean partial recovery of the ability of PTH secretion toward normality. The degree of reinnervation may have impacted our results. This raises the argument that subtotal PTX may have the advantage of preserving local nervous system inputs in the remaining parathyroid gland.

We also speculated if the number of fragments implanted could have influenced our results. Santos *et al.*[28] tried to select which factors were related to grafts hypofunction in patients with renal hyperparathyroidism submitted to total PTX with AT after 1 year of surgery. They evaluated patient´s gender and weight, preoperative levels of calcium, phosphorus and PTH, post-operative amounts of calcitriol ingested, number of fragments and histology of the implanted glands. The results showed that the number of fragments was not related to parathyroid graft´s hypofunction as well as the other factors evaluated.

Strategies to avoid definitive hypoparathyroidism include reimplant of cryopreserved parathyroid tissue.[29] These patients are also at risk of developing adynamic bone disease.[30] However, considering the poor response of grafted parathyroid tissue during induced hypocalcemia observed in this study, other therapeutic approaches should be considered. Choosing subtotal parathyroidectomy with posterior clinical management of hypercalcemia if needed (perhaps with calcimimetics or other drugs) might be an option.

Limitations of this study are related to: the small number of patients, serum vitamin D levels not measured, controls were younger than patients (results were the same even if corrected by age-data not shown) and the rate of change between baseline calcium and the nadir point among groups was different (decrease of 12.1% in controls and 6.8% in patients). This difference occurred probably because patient´s baseline pH was lower (patients were more acidotic than controls). However, induced hypocalcemia was significant for each group. Additionally, the authors included both transplanted and dailysis patients in the same group for testing. The reason for that was the homogeneous absence of PTH response during induced hypocalcemia in all subjects and the small number of dialysis patients (three individuals).

Conclusion

The assessment of grafted parathyroid tissue secretory capacity after total PTX with AT during bicarbonate induced hypocalcemia revealed a blunted response with no changes in iPTH levels within 6-12 months after surgery. More studies are needed to define the ideal surgical technique and to better understand heterotopic parathyroid function.

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