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A RANDOMIZED STUDY COMPARING PARATHYROIDECTOMY VERSUS CINACALCET TO TREAT HYPERCALCEMIA IN KIDNEY ALLOGRAFT RECIPIENTS WITH HYPERPARATHYROIDISM.

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ABSTRACT

Persistent secondary hyperparathyroidism is a common cause of hypercalcemia after kidney transplantation. Oral cinacalcet corrects hypercalcemia although parathyroidectomy seems to be more cost-effective. This study was designed to evaluate whether subtotal parathyroidectomy was superior to cinacalcet to control hypercalcemia due to persistent hyperparathyroidism after kidney transplantation. This is a 12 month, prospective, multicenter, open-label randomized study. Kidney allograft recipients with hypercalcemia and elevated intact parathyroid hormone (iPTH) were eligible if they were at least six months after transplantation and showed estimated glomerular filtration rate >30 ml/min/1.73 m^2. Primary end point was proportion of patients with normocalcemia at 12 months. Secondary end points were serum iPTH, serum phosphate, bone mineral density, vascular calcification, renal function, patient and graft survival and economic cost. A total of 30 patients were randomized to receive cinacalcet (N=15) or parathyroidectomy (N=15). The proportion of patients achieving normocalcemia at 12 months was 10/15 in cinacalcet and 15/15 in parathyroidectomy group (P=0.04). Normalization of serum phosphate was observed in almost all patients. Parathyroidectomy induced higher reduction of iPTH and was associated with a significant increase in femoral neck bone mineral density while vascular calcification remained unchanged in both groups. Most frequent adverse events were digestive intolerance in cinacalcet and hypocalcemia in parathyroidectomy. Surgery would be more cost effective if cinacalcet duration reached 14 months. All patients were alive and with a functioning graft at the end of follow-up. In conclusion, parathyroidectomy seems superior to cinacalcet to control hypercalcemia in kidney transplant patients with persistent hyperparathyroidism.

INTRODUCTION

Kidney transplantation is the best therapeutic option for ESRD patients (1). Improvements in transplant care and new immunosuppressive drugs have led to progressive increase in short-term graft survival (2). However, long-term outcome has not increased accordingly because of progressive chronic allograft damage and patient death (3). Persistent secondary hyperparathyroidism has been associated with both chronic allograft nephropathy (4) and cardiovascular morbidity and mortality after kidney transplantation (5, 6).

Secondary hyperparathyroidism is a common complication in chronic kidney disease. Parathyroid glands are committed to secrete parathyroid hormone (PTH) in order to correct calcium and phosphate serum levels. However, progressive decline in glomerular filtration rate (GFR) overcomes the compensatory capacity of PTH. Continuous stimulation on parathyroid tissue induces relevant pathogenic abnormalities as down-regulation of the vitamin D receptor and calcium-sensing receptor, which result in the loss of PTH calcium-dependent autoregulation (7). Indeed, parathyroid glands become hyperplasic and even adenoma transformation can be developed. Kidney transplantation rapidly restores GFR and the renal capacity to respond to PTH, that is phosphaturia and tubular calcium reabsortion (8,9). Usually, some degree of autoregulation is preserved with progressive PTH reduction and regression of parathyroid hyperplasia in few months after transplantation. However, in 20-30% of cases parathyroid gland resistance to inhibitory feedback persisted several years after transplantation (9) and inappropriate high PTH levels are associated with hypercalcemia, hypophosphatemia, renal allograft calcifications and dysfunction, loss of

bone mineral density and increased risk of fracture, vascular calcification and increased risk of cardiovascular events (10, 11, 12, 13). These cases are named tertiary hyperparathyroidism or persistent hyperparathyroidism after kidney transplantation.

Long-term clinical management is rather controversial and very limited due to hypercalcemia that can be aggravated by vitamin D supplementation or by vitamin D analogs (14, 15). Subtotal parathyroidectomy has been considered until recently the only therapeutic approach. However, it is an invasive procedure with potential surgical complications, sometimes being difficult to determine the precise amount of gland to be removed (16). Therefore, a surgical expertise is critical in order to minimize complications and to reduce the risk of hypoparathyrodism and unsatisfactory reduction of PTH. Physicians and patients are reluctant to indicate or to accept parathyroidectomy (17,18), especially after the appearance of cinacalcet into the clinics. Cinacalcet (Mimpara®, Amgen Inc., CA) is an allosteric modulator of the calcium-sensing receptor that is able to reduce PTH and calcium in patients on dialysis with secondary hyperparathyroidism (19). In a recent clinical trial performed in renal transplant recipients with persistent hyperparathyroidism it has been demonstrated that cinacalcet is superior to placebo in order to correct hypercalcemia and hypophosphatemia (20). However, there are no clinical studies comparing cinacalcet vesus parathyroidectomy in this setting.

RESULTS

Study population

Thirty-seven patients fulfilling criteria were assessed for eligibility. Seven patients were screening failure (3 withdraw consent before any study procedure and 4 had laboratory values during screening visit that did not comply with inclusion/exclusion criteria. A total of 30 patients were randomized (intention to treat population) to receive cinacalcet (N=15) or parathyroidectomy (N=15). Table 1 shows patient baseline main clinical characteristics. Patients were included in the study a mean time of 45 months after transplantation. Regarding maintenance immunosuppression 15 out of 30 were on steroid-free regime and 24 out of 30 were on tacrolimus. All patients on steroids were receiving 5 mg per day without modification during the study. There were 2 patients on cyclosporine (one in each arm) and 4 patients on sirolimus (2 in each arm). All patients were on mycophenolate.

All patients started with cinalcalcet 30 mg/d and then adjusted to accomplish normocalcemia. At month 3, cinacalcet doses were 60 mg/d (33%) and 30 mg/d (67%) and at month 12, 60 mg/d (36%) and 30 mg (64%). One patient discontinued cinalcalcet at month 3 due to oral intolerance. Surgical iPTH reduction was assessed during surgical procedure (Figure 1). The % of iPTH decline ten minutes after parathyroid gland removal ranged within 75.1 and 97.7%.

Baseline serum calcium, phosphate, iPTH and calcidiol serum levels as well as eGFR and proteinuria were similar between both groups (Table 2).

Primary end point

The proportion of patients achieving the objective of normocalcemia (serum calcium <2.55 mmol/L) at 12 months was 10/15 (67%) in cinacalcet and 15/15 (100%) in

parathyroidectomy group (P=0.04). The evolution of calcium serum levels is depicted in Figure 2A and Table 2.

Secondary end points

The evolution of serum iPTH is showed in Figure 2B. iPTH was similar in both groups at baseline. The reduction of iPTH was significantly higher in parathyroidectomy than in cinacalcet. iPTH within 1.13-7.11 pmol/L at 12 month was accomplished in 0/15 in cinacalcet versus 10/15 after parathyroidectomy. Normalization of serum phosphate at month 12 (0.85 to 1.5 mmol/L) was achieved in 14/15 in cinacalcet and 15/15 in parathyroidectomy, although values tended to be higher in the parathyroidectomy group (Figure 2C).

Markers of bone turnover are showed in Table 2. Bone-specific alkaline phosphase decreased over-time in both groups. However, osteocalcin and C-terminal telopeptide tended to be lower in parathyroidectomy than in cinacalcet group. Calcidiol levels increased over time only after parathyroidectomy as the majority of patients received oral calcium and vitamin D supplementation early after surgery in order to prevent hypocalcemia due to hungry bone syndrome. Interestingly, only parathyroidectomy was associated with a significant improvement in bone mineral density at 12 month, in particular in femoral neck as showed in Table 3.

Evolution of eGFR and proteinuria is showed in Table 2. There was some degree of eGFR loss in both groups without increase in proteinuria. During 12-month follow-up, eGFR decline was 9 ml/min in the cinacalcet and 4 ml/min GFR in the parathyroidectomy group (Figure 3).

We performed assessment of vascular calcification by CT at baseline, 6 and 12 month. No differences were observed between groups at baseline and calcification score remained unchanged during follow-up (Table 2, Figure 4).

Safety

One patient in the cinacalcet group discontinued the drug due to digestive intolerance and severe xerostomia. Adverse events in the cinacalcet arm were diarrhea (n=2), edema (n=2), urinary tract infection (n=2) and renal dysfunction (n=2). Adverse events in parathyroidectomy group were hypocalcemia (n=4), traumatic tibial fracture (n=1), diarrhea (n=3), transient dysphonia (n=2) and intraductal breast cancer (n=1). There were 2 patients requiring hospitalization due to severe hypocalcemia after parathyroidectomy whereas one patient was admitted to the hospital in the cinacalcet group because of severe diarrhea. All patients were alive and with a functioning graft at the end of follow-up.

Economic study

We calculated the economic cost of both therapies to the Catalan Health Service. In the parathyroidectomy group we included: parathyroid gland scintigraphy, neck ultrasound, preoperative assessment, surgical, anesthetic and hospitalization cost, pathological report, rehospitalization cost, calcium and vitamin D supplies. In the cinacalcet group we included: parathyroid gland scintigraphy, rehospitalization cost and cinacalcet therapy. One-year cost per patient was 3712.27 euros in the parathyroidectomy group and 3257.96 euros in the cinacalcet group (12% higher in parathyroidectomy). Therefore, if cinacalcet treatment duration reached at least 14 months, parathyroidectomy would be considered superior in terms of cost-effectiveness.

DISCUSSION

This study shows that standard of care subtotal parathyroidectomy is superior to cinacalcet to correct hypercalcemia in renal allograft recipients with persistent hyperparathyroidism. All patients with parathyroidectomy and nearly 70% with cinacalcet achieved normocalcemia. Moreover, the reduction of iPTH was higher in parathyroidectomy than in the cinacalcet group. Accordingly, only parathyroidectomy was associated with a significant improvement in bone mineral density at femoral neck.

A recent clinical trial demonstrated that cinacalcet in comparison to placebo is a highly effective treatment option for correcting serum calcium levels among this population (20). Our results in the cinacalcet arm were similar since the majority of patients achieved normal serum calcium and phosphate levels. Also, in both studies cinacalcet reduced iPTH, although it persisted above normal range in a high proportion of patients. The primary objective in both studies is to achieve normocalcemia. In the cinacalcet arm this can be achieved in the majority of cases with mild iPTH reduction. The high level of the bone turnover biomarker C-terminal telopeptide throughout the study suggests that persistence of hyperparathyroidism could be the potential explanation for the lack of improvement in bone mineral density in patients treated with cinacalcet (20). Alternatively, given the high prevalence of low bone turnover in transplant recipients with hypercalcemia and hyperparathyroidism, it has been suggested that cinacalcet or even parathyroidectomy may exacerbate bone disease (21). In our study, parathyroidectomy was associated with improvement in bone mineral density and regulation of biomarkers of high bone turnover. The cause would be iPTH normalization and/or the oral calcium and vitamin D supplementation given after

parathyroidectomy to prevent hypocalcemia associated with hungry bone syndrome, as confirmed by a significant increase in calcidiol levels (14, 22). Further studies with cinacalcet in combination with vitamin D in which iPTH correction would be the primary end point are needed to properly ask this question.

Vascular calcification is an important complication in patients with secondary hyperparathyroidism (23). We observed similar results in cinacalcet and parathyroidectomy groups, both treatments were associated with no progression in vascular calcification. Parathyroidectomy was not associated with regression of vascular calcification despite to achieve nearly full correction of serum calcium and iPTH. This fact suggests that vascular calcification is not reversible, at least in the short-term, and reinforces the importance of preventing bone mineral disorders in early stages of chronic kidney diseases.

There are some previous studies suggesting that both cinacalcet and parathyroidectomy were associated with decrease in renal function (17, 24). However, this effect was not observed in the previous cinacalcet clinical trial (20) and long-term graft outcome was not affected by parathyroidectomy (24). A renal hemodynamic mechanism was suggested since iPTH has a known positive regulatory effect on renal perfusion and GFR that can be abrogated by intervention therapies (25). In our study GFR decline was higher in cinacalcet than in parathyroidectomy. Previous studies showed association between high iPTH levels, kidney allograft interstitial calcification and loss of renal function, providing a rationale to our finding (26). However, we did not perform protocol biopsies to corroborate this hypothesis.

As previously reported, the most frequently reported adverse event in the cinacalcet group was digestive intolerance (27), being a limitation to increase cinacalcet dose sufficiently to achieve serum calcium correction. Complications of parathyroidectomy depend on both surgical experience and procedure itself (28). A recent study reviewed early outcomes of 4435 dialysis patients who underwent parathyroidectomy (29) and reported 2% mortality and 23.8% rehospitalization at 30 days after discharge. Nevertheless, other studies have shown that successful parathyroidectomy may reduce the risk for all-cause and cardiovascular mortality in dialysis patients (30, 31). In order to minimize surgical bias, the same surgical team performed all parathyroidectomies. A minimal invasive procedure with assessment of early drop in iPTH to ascertain that enough parathyroid gland tissue had been removed was carried out. In our study early rehospitalization was 13% after parathyroidectomy and 7% in cinacalcet. As expected, main complications after parathyroidectomy were hypocalcemia, some of them related to oral intolerance to high calcium doses and transient dysfonia due to recurrent laryngeal nerve mild surgical traumatism.

There is a paucity of data regarding of the optimal management of persistent post renal transplant hyperparathyroidism (21). A cost-utility analysis has been reported comparing parathyroidectomy with cinacalcet in dialysis patients with severe hyperparathyroidism (32). This study concluded that surgery was more cost-effective if cinacalcet treatment duration reached 16 months. Our study provides similar results in the renal transplantation setting, as the one-year economic cost associated with both treatments is similar, suggesting that parathyroidectomy is more cost-effective in the long-term.

Our study has some limitations. First, follow-up is probably too short for providing relevant information about fracture risk, vascular calcification and recurrence of hyperparathyroidism after parathyroidectomy. Second, cinacalcet dosage was adjusted to achieve normocalcemia without taking into account iPTH reduction. Third, the fact that the same surgeon performed all parathyroidectomies could be a limitation to make a general recommendation. Finally, in the absence of bone biopsies it may be difficult to ascertain bone turnover in renal transplant patients (33). Nevertheless, taking into account that our results in the cinacalcet arm are similar to those previously reported (20) and that extended minimally invasive parathyroidectomy is a feasible approach (34) our results could reasonably be reproduced in a big clinical trial.

In conclusion, both cinacalcet and parathyroidectomy are effective to control hypercalcemia due to persistent hyperparathyroidism after kidney transplantation. However, parathyroidectomy seems to be superior to cinacalcet in terms of proportion of patients achieving calcium and iPTH normalization, increase in bone mineral density and cost-effectiveness. Therefore, our results suggest that in renal allograft recipients with hypercalcemia due to persistent hyperparathyroidism, parathyroidectomy could be the first-line therapy whereas cinacalcet may be indicated in those patients with surgical contraindication.

CONCISE METHODS

Study population

This was an investigator promoted, prospective, multicenter, open-label and randomized study performed in renal allograft recipients with hypercalcemia due to post transplant persistent hyperparathyroidism. The study was approved by The Spanish Drug Agency (EudraCT 2008-007017-76) and registered in Clinical Trials (NCT01178450).

Inclusion criteria were defined as follows: patients with a functioning renal graft with an estimated GFR ≥30ml/min; at least 6 months after kidney transplantation; serum intact PTH (iPTH) levels ≥15 pmol/L; corrected total serum calcium levels ≥2.63mmol/L and serum phosphate levels ≤1.2 mmol/L. Patients not meeting the inclusion criteria or with a contraindication to surgery or cinacalcet treatment were excluded from the trial. Patients were included in the trial after providing written informed consent by signing an Ethics Committee approved document, in accordance to Good Clinical Practices. During Screening period, a complete laboratory assessment was performed (including iPTH, calcium and phosphate serum levels) to verify that patient met inclusion/exclusion criteria. At baseline, a parathyroid gammagraphy was performed to discard ectopic parathyroid tissue. Women of child bearing potential were tested for pregnancy at screening visit to discard pregnancy and were informed to avoid pregnancy during the study. Patients that did not meet inclusion/exclusion criteria after the screening period were considered as screening failure and not included in the statistical analysis.

Study groups

Patients were randomized 1:1 to receive cinacalcet oral treatment or undergo a subtotal parathyroidectomy. Parathyroidectomy was performed in all cases by the same surgeon

(PM) and at Bellvitge Hospital. Briefly, the neck was explored bilaterally and all parathyroid glands identified and removed leaving a remnant equivalent to 1 normal gland in size (50 mg). A perioperatively pathological assessment was performed in all cases. A systematic transcervical thymectomy was also added in order to prevent persistent disease secondary to a fifth gland that could be present in up to 15% of patients. Intraoperative iPTH assessment was measured at baseline and 10 minutes after subtotal parathyroidectomy.

Patients assigned to cinacalcet group started with 30 mg/day, and then adjusted to achieve the objective of normocalcemia. Patients assigned to the parathyroidectomy group were scheduled to undergo surgery within 3 months, with a previous neck ultrasound and preoperative screening. Patients were followed during 12 months after the initiation of cinacalcet treatment or after parathyroidectomy. Study visits were performed at baseline, 3, 6 and 12 months. All patients randomized were considered as intention to treat population and included in the data analysis.

Primary and secondary efficacy endpoints

Primary end point was proportion of patients with normocalcemia at 12 months. Secondary end points were serum iPTH, serum phosphate, bone turnover biomarkers bone mineral density (BMD) and vascular calcification, renal function, patient and graft survival and economic cost of associated with each treatment.

Serious and non-serious adverse events were monitored through all the length of the study and reported accordingly. BMD was evaluated at baseline and month 12 at femoral neck, lumbar spine and distal 1/3 radius by dual X-ray absorptiometry centrally at Bellvitge Hospital. Vascular calcification evaluation was performed at baseline, 6 and 12 month and centralized at Bellvitge Hospital. Patients underwent thoracic, abdominal

and pelvis unenhanced CT scan. The images obtained were assessed for calcification detection and scoring by a radiologist (RM). Imaging was performed using a 16-slice or 64-slice CT system (General Electric). 1,25mm slices were obtained of the thorax, abdomen and pelvis with posterior 0,625mm thin reconstructions. All the images generated were analyzed using a GE workstation. Images were analyzed using a window preset of ‘‘bone’’. The level of the aortic arch was chosen as the starting point. From that point we analyzed the supraaaortic trunks (origin of subclavia and carotid arteries), ascending aorta, descending thoracic aorta, diaphragmatic aorta, origin of the celiac trunk and superior mesenteric artery, suprarenal, renal, infrarenal, aortic bifurcation, right and left iliac bifurcation and both proximal femoral arteries. The score was obtained on axial CT images. For each section a value of 0 was given for the absence of calcification deposit, 1 for presence of plaques and 2 if more than 4 plaques were detected. An extra point was given when the plaque occupied more than 50% of the arterial circumference and 2 points when was covering the entire circumference. Finally 1 extra point was assigned when the thickness of the plaque was superior to 4 mm in any of the deposits detected. Based on that system the final score could be between 0 and 80. Stability or progression of calcifications deposits were achieved comparing the three CT scans performed for each patient.

Statistical analysis

A sample size of 30 subjects (15 per arm) was estimated to provide 80% power to achieve a statistical significance of 0.05 (one-sided) using the chi-square test. This assumed a response rate for normocalcemia of 65% in cinacalcet and 95% in parathyroidectomy. Differences in the categorical variables between both groups were calculated by means of the $\chi 2$ test or the Fisher’s exact test. The differences in the

quantitative variables including the main variable between groups were calculated by means of the Student's t-test or the Mann–Whitney U-test. A P-value <0.05 was considered significant for all test. Results were depicted as mean ± standard deviation.

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Statement of competing financial interest

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FIGURE LEGENDS

Figure 1. Assessment of iPTH decline early after parathyroidectomy. iPTH was measured at baseline and 10 minutes after surgery to assure that enough parathyroid gland tissue had been removed.

Figure 2. Serum calcium (A), iPTH (B) and phosphate (C) evolution in cinacalcet and parathyroidectomy groups. Both treatments are associated with correction of calcium and phosphate although the reduction of iPTH was higher in parathyroidectomy than in cinacalcet group.

Figure 3. Estimated GFR at baseline and month 12 in cinacalcet and parathyroidectomy groups. Decline in renal function was higher in cinacalcet than in parathyroidectomy group.

Figure 4. A representative case to assess changes in vascular calcification. Unenhanced CT scan at the level of the aortic arch in the same patient at baseline (A), at 6 months (B) and at 12 months (C). Multiples plaques are seen (arrows) with no variation during the follow up. Calcification value at this level was 3 in all three time-points.

Table 1. Patient baseline characteristics

	All patients (N=30)	Cinacalcet (N=15)	Parathyroidectomy (N=15)	P value
Age (years)	53.9±12.4	55.0±13.6	53.0±11.8	0.67
Sex (M/F)	13/17	7/8	6/9	0.71
Time in dialysis (months)	38.8±29.2	33.5±26.9	44.1±32.5	0.39
Cause of ESRD				
Diabetes	2	1	1	
Hypertension	4	2	2	
Glomerulonephritis	5	2	3	
APKD	5	3	2	
Other	14	7	7	
Previous transplant (yes/no)	4/26	2/13	2/13	1.00
Time after kidney transplantation (months)	45.5±39.9	46.5±42.2	44.4±38.8	0.89
Blood pressure (mmHg)				
Systolic	140±20	136±22	147±16	0.13
Diastolic	82±14	80±11	84±16	0.33
Steroid treatment (yes/no)	15/15	7/8	8/7	0.90
Tacrolimus (yes/no)	24/6	12/3	12/3	1.00

Table 2. Evolution of serum calcium, phosphate, iPTH, biomarkers of bone turnover, renal function and vascular calcification in cinacalcet and parathyroidectomy groups

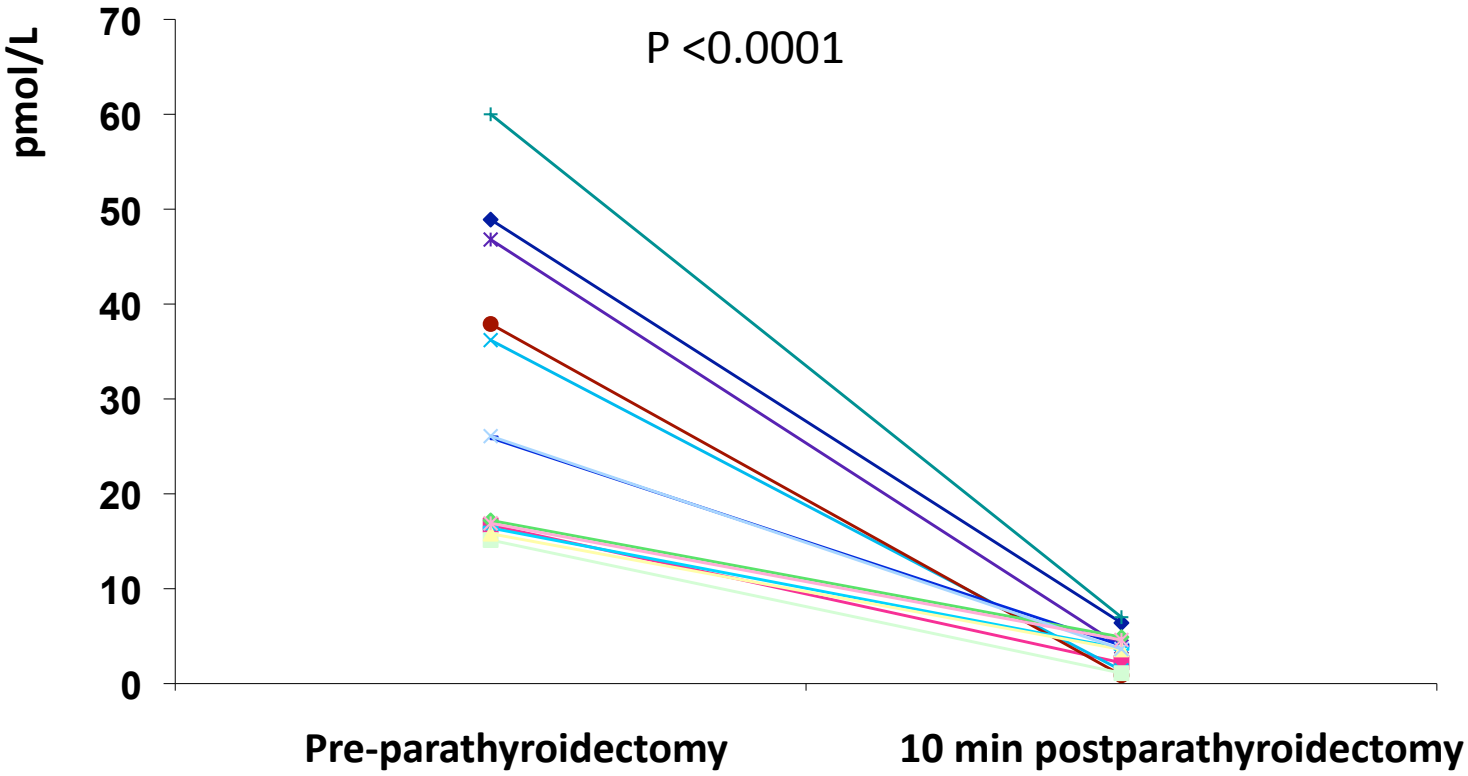
	Cinacalcet				Parathyroidectomy			
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Baseline**	**Month 3**	**Month 6**	**Month 12**
Albumin (g/L)	43.9±2.8	44.1±1.9	43.9±2.5	43.7±3.1	44.5±2.4	44.4±2.8	44.1±3.3	43.4±3.0
Calcium (mmol/L)	2.72±0.1	2.42±0.2[a]	2,42±0.2[a]	2.37±0.2[a]	2.78±0.2	2.28±0.2[b]	2.26±0.2[b]	2.22±0.2[b]
iPTH (pmol/L)	25±12	18±7[a]	20±9[a]	22±11	37±18	9±10[b]	7±6[b]	6±5[b]
Phosphorus (mmol/L)	0.92±0.2	1.1±0.1[a]	1.0±0.2[a]	1.1±0.1[a]	0.93±0.2	1.3±0.2[b]	1.3±0.2[b]	1.3±0.3[b]
25(OH)D3 (nmol/L)	51±24	57±21	59±21	53±15	41±14	90±32[b]	79±31[b]	70±30[b]
C-terminal telopeptide (µg/L)	0.48±0.22	0.72±0.44[a]	0.72±0.35[a]	0.71±0.45[a]	0.48±0.27	0.26±0.24[b]	0.13±0.14[b]	0.33±0.35[b]
alkaline phosphatase (µKat/L)	2.2±1.7	2.2±1.1	2.2±1.2	1.5±0.5[a]	1.9±0.9	2.2±1.6	1.8±1.2	1.7±1.1[b]
Osteocalcin (µg/L)	32±16	41±23	37±17	40±27	28±19	25±18	25±8	22±13[b]
eGFR (ml/min)	57±11	54±16	53±6	48±14[a]	57±16	52±14	53±17	53±14
Proteinuria (mg/d)	195±150	144±110	171±135	200±169	243±150	264±273	234±229	251±362
Abdominal aorta calcification score	4.9±3.4	-	5.1±3.8	5.2±3.9	4.9±3.8	-	5.0±3.8	5.0±3.8
Vascular calcification score	17.0±13.5	-	18.6±13.8	18.8±14.2	17.7±12.7	-	17.3±13.7	17.6±13.7

[a]P<0.05 vs Baseline in cinacalcet group
[b]P<0.05 vs Baseline in parathyroidectomy group

Table 3. Bone mineral density (BMD) at baseline and month 12 with percent change BMD calculated in parathyroidectomy and cinacalcet groups

	Parathyroidectomy	Cinacalcet	P value
BMD Baseline			
Femoral neck (g/cm2)	0.819 ± 0.164	0.723 ± 0.089	0.12
Lumbar spine (g/cm2)	0.993 ± 0.227	0.904 ± 0.106	0.25
Distal 1/3 radius (g/cm2)	0.613 ± 0.097	0.661 ± 0.116	0.30
BMD month 12			
Femoral neck (g/cm2)	0.846 ± 0.149	0.700 ± 0.081	0.01
Lumbar spine (g/cm2)	1.015 ± 0.213	0.896 ± 0.109	0.11
Distal 1/3 radius (g/cm2)	0.630 ± 0.086	0.658 ± 0.114	0.52
% Change at month 12			
Femoral neck (%)	+ 3.8 ± 6.1	- 3.0 ± 5.1	0.012
Lumbar spine (%)	+ 2.7 ± 7.8	- 0.9 ± 4.7	0.206
Distal 1/3 radius (%)	+ 3.3 ± 6.6	- 0.4 ± 2.6	0.096

Figure 1. Assessment of iPTH decline early after parathyroidectomy



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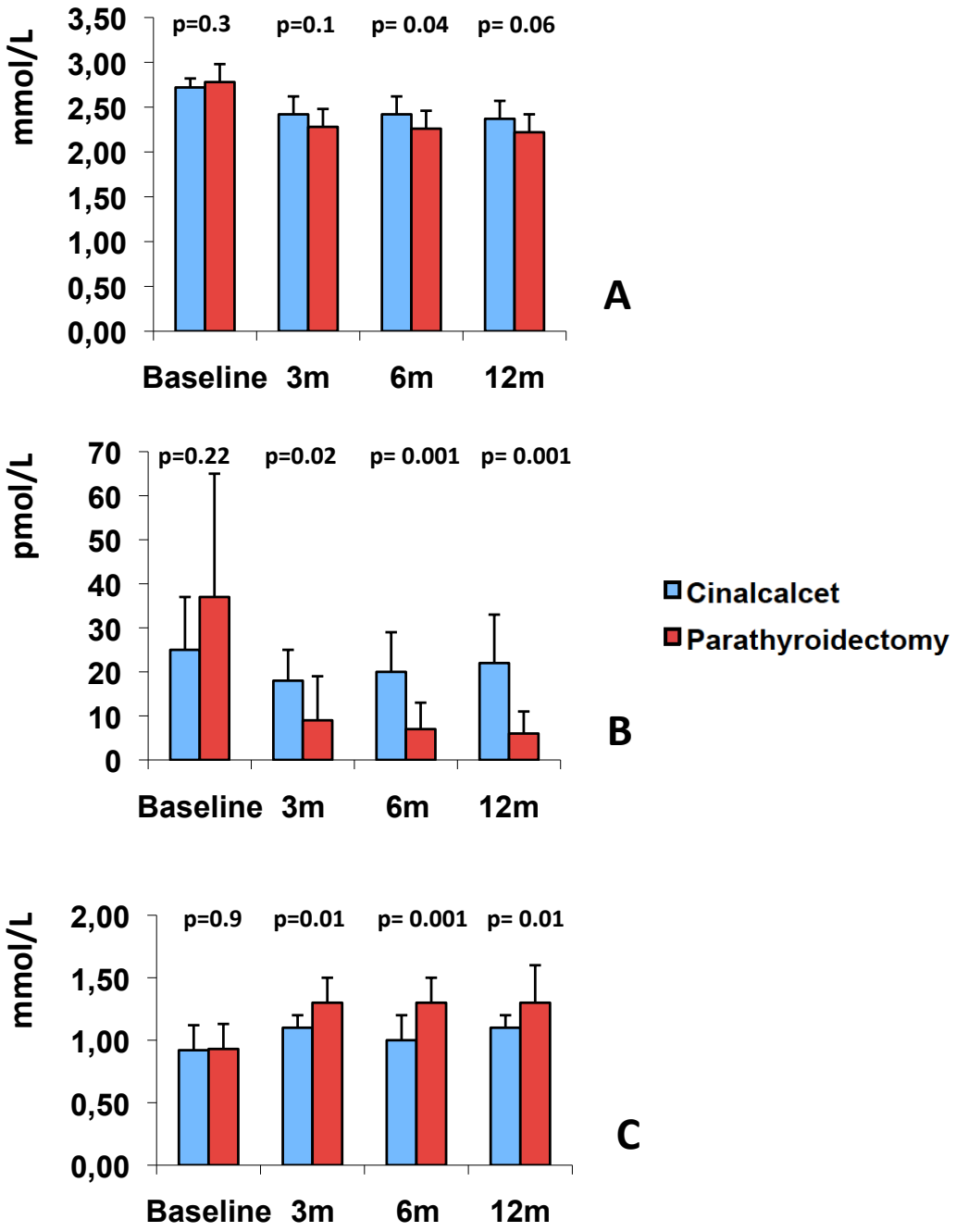
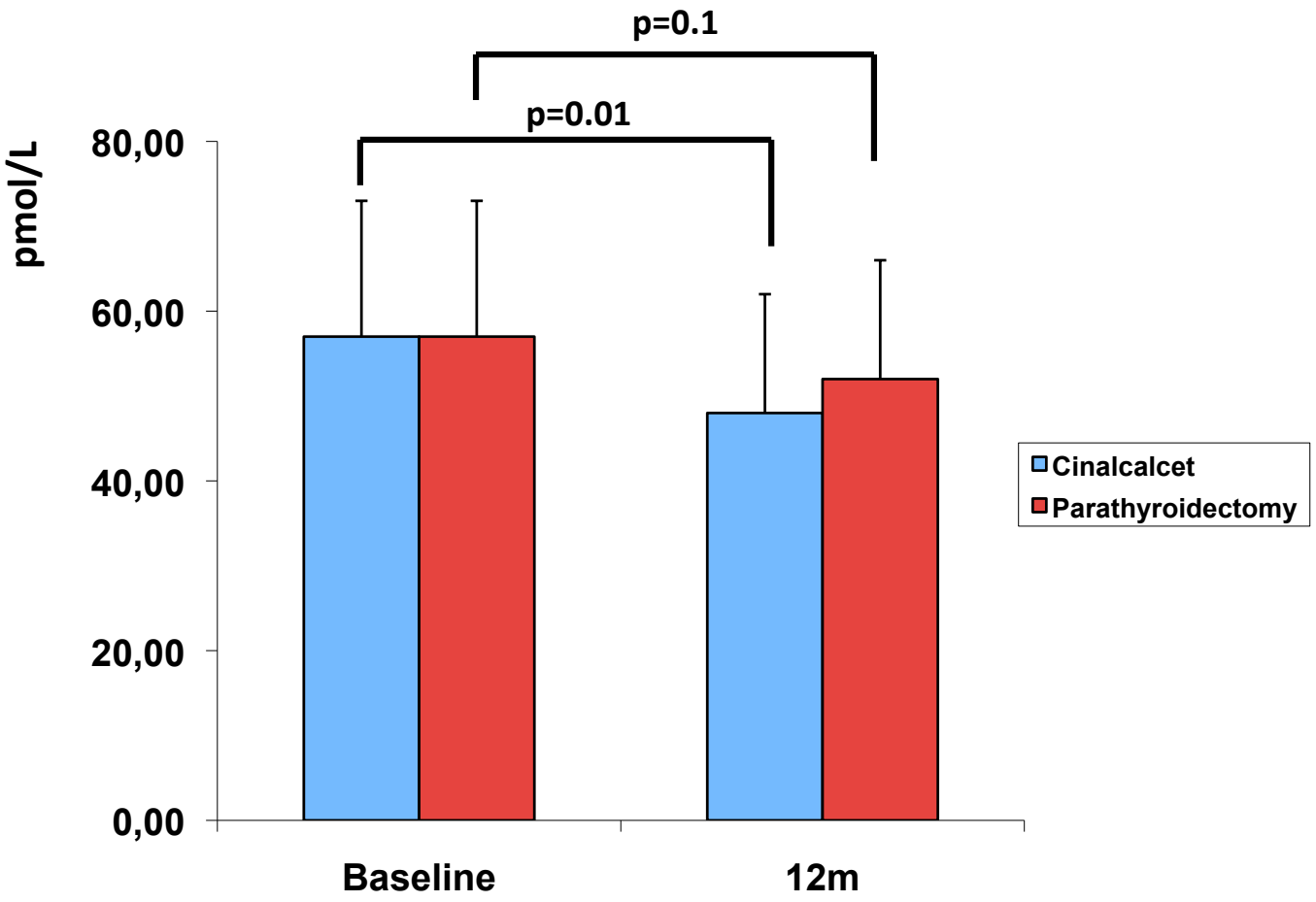


Figure 3. Estimated GFR at baseline and month 12 in cinacalcet and parathyroidectomy groups



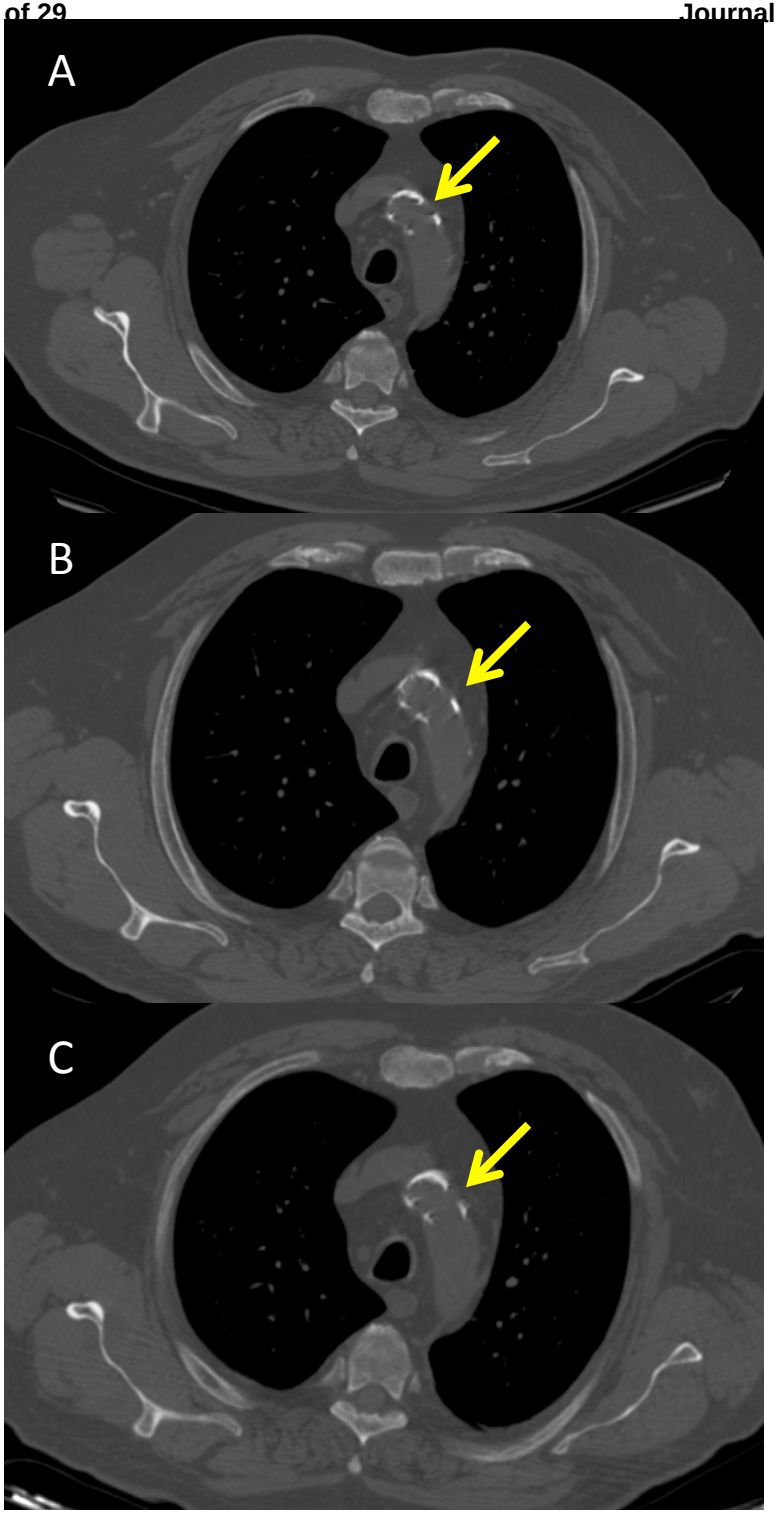


Figure 4. A representative case to assess changes in vascular calcification