A Randomized Study Comparing Parathyroidectomy with Cinacalcet for Treating Hypercalcemia in Kidney Allograft Recipients with Hyperparathyroidism

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ABSTRACT

Tertiary hyperparathyroidism is a common cause of hypercalcemia after kidney transplant. We designed this 12-month, prospective, multicenter, open–label, randomized study to evaluate whether subtotal parathyroidectomy is more effective than cinacalcet for controlling hypercalcemia caused by persistent hyperparathyroidism after kidney transplant. Kidney allograft recipients with hypercalcemia and elevated intact parathyroid hormone (iPTH) concentration were eligible if they had received a transplant ≥6 months before the study and had an eGFR>30 ml/min per 1.73 m^2. The primary end point was the proportion of patients with normocalcemia at 12 months. Secondary end points were serum iPTH concentration, serum phosphate concentration, bone mineral density, vascular calcification, renal function, patient and graft survival, and economic cost. In total, 30 patients were randomized to receive cinacalcet (*n*=15) or subtotal parathyroidectomy (*n*=15). At 12 months, ten of 15 patients in the cinacalcet group and 15 of 15 patients in the parathyroidectomy group (*P*=0.04) achieved normocalcemia. Normalization of serum phosphate concentration occurred in almost all patients. Subtotal parathyroidectomy induced greater reduction of iPTH and associated with a significant increase in femoral neck bone mineral density; vascular calcification remained unchanged in both groups. The most frequent adverse events were digestive intolerance in the cinacalcet group and hypocalcemia in the parathyroidectomy group. Surgery would be more cost effective than cinacalcet if cinacalcet duration reached 14 months. All patients were alive with a functioning graft at the end of follow-up. In conclusion, subtotal parathyroidectomy was superior to cinacalcet in controlling hypercalcemia in these patients with kidney transplants and persistent hyperparathyroidism.

Kidney transplantation is the best therapeutic option for patients with ESRD.[1] Improvements in transplant care and new immunosuppressive drugs have led to a 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 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 CKD. Parathyroid glands are committed to secrete parathyroid hormone (PTH) to correct calcium and phosphate serum levels. However, progressive decline in GFR overcomes the

Table 1. Patient baseline characteristics

Variable	All Patients (n=30)	Cinacalcet (n=15)	Subtotal Parathyroidectomy (n=15)	P Value
Age, yr	53.9±12.4	55.0±13.6	53.0±11.8	0.67
Sex, men/women	13/17	7/8	6/9	0.71
Time on dialysis, mo	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	
GN	5	2	3	
ADPKD	5	3	2	
Other	14	7	7	
Previous transplant, yes/no	4/26	2/13	2/13	>0.99
Time after kidney transplantation, mo	45.5±39.9	46.5±42.2	44.4±38.8	0.89
BP, 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	>0.99

Data is displayed as means±standard deviation and number of cases/events. ADPKD, autosomical dominant polycystic kidney disease.

compensatory capacity of PTH. Continuous stimulation on parathyroid tissue induces relevant pathogenic abnormalities as downregulation 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 can be developed. Kidney transplantation rapidly restores GFR and the renal capacity to respond to PTH (that is, phosphaturia and tubular calcium reabsorption).[8,9] Usually, some degree of autoregulation is preserved with progressive PTH reduction and regression of parathyroid hyperplasia a few months after transplantation. However, in 20%–30% of patients, parathyroid gland resistance to inhibitory feedback persisted several years after transplantation,[9] and inappropriately high PTH levels are associated with hypercalcemia, hypophosphatemia, renal allograft calcifications and dysfunction, loss of bone mineral density (BMD) and increased risk of fracture, vascular calcification, and increased risk of cardiovascular events.[10–13] These patients are diagnosed with tertiary hyperparathyroidism or persistent hyperparathyroidism after kidney transplantation.

Long–term clinical management is rather controversial and very limited because of hypercalcemia that can be aggravated by vitamin D supplementation or 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, because it is sometimes difficult to determine the precise amount of gland to be removed.[16] Therefore, a surgical expertise is critical to minimize complications and reduce the risk of hypoparathyroidism and unsatisfactory reduction of PTH. Physicians and patients are reluctant to indicate or accept subtotal parathyroidectomy,[17,18] especially after the appearance of cinacalcet into the clinics. Cinacalcet (Mimpara; Amgen Inc., Thousand Oaks, 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 renal transplant recipients with tertiary hyperparathyroidism, a recent clinical trial showed that cinacalcet is superior to placebo at correcting hypercalcemia and hypophosphatemia.[20] However, there are no clinical studies comparing cinacalcet with subtotal parathyroidectomy in this setting.

RESULTS

Study Population

Thirty-seven patients fulfilling criteria were assessed for eligibility. Seven patients were screening failures (three withdrew consent before any study procedure, and four had laboratory values during that screening visit that did not comply with inclusion/exclusion criteria). In total, 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 of 30 were on a steroid-free regime, and 24 of 30 were on tacrolimus. All patients on steroids were receiving 5 mg/d prednisone without modification during the study. There were two patients on cyclosporin (one in each arm) and four patients on sirolimus (two in each arm). All patients were on mycophenolate.

In the cinacalcet group, the starting cinacalcet dose was 30 mg/d, and then, it was adjusted to accomplish normocalcemia. At month 3, cinacalcet doses were 60 mg/d (33%) and 30 mg/d (67%), and at month 12, they were 60 mg/d (36%) and 30 mg/d (64%). One patient discontinued cinacalcet at month 3 because of oral intolerance. Surgical intact parathyroid hormone (iPTH) reduction was assessed during the surgical procedure (Figure 1). The iPTH decline 10 minutes after parathyroid gland removal ranged between 75.1% and 97.7%.
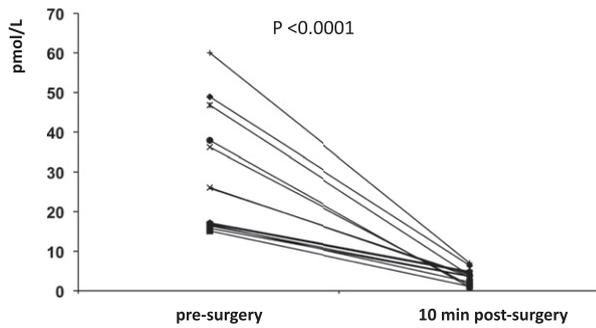
Figure 1. The iPTH decline early after subtotal parathyroidectomy was higher than 75%. Assessment of iPTH decline early after subtotal parathyroidectomy. iPTH was measured at baseline and 10 minutes after surgery to assure that enough parathyroid gland tissue had been removed.

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 normo-calcemia (serum calcium within 2.22–2.55 mmol/L) at 12 months was ten of 15 (67%) in the cinacalcet group and 15 of 15 (100%) in the parathyroidectomy group (P=0.04). The evolution of calcium serum levels is depicted in Figure 2A and Table 2. A major limitation to increase cinacalcet dose to achieve normo-calcemia in the cinacalcet group was digestive intolerance.

Secondary End Points

The evolution of serum iPTH is shown in Figure 2B. iPTH was similar in both groups at baseline. The reduction of iPTH was significantly greater in the parathyroidectomy group than in the cinacalcet group. Normalization of iPTH (serum iPTH within 1.13–7.11 pmol/L) at 12 months was accomplished in zero pf 15 in the cinacalcet group versus ten of 15 after subtotal parathyroidectomy (P=0.002). iPTH values in five patients in the parathyroidectomy group who did not achieve a normal level were 0.32, 7.9, 8.9, 17.3, and 15.48 pmol/L. Normalization of serum phosphate at month 12 (0.85–1.5 mmol/L) was achieved in 14 of 15 in the cinacalcet group and 15 of 15 in the parathyroidectomy group, although serum phosphate values at 3, 6, and 12 months were higher in the parathyroidectomy group (Figure 2C).

Markers of bone turnover are shown in Table 2. Bone–specific alkaline phosphatase decreased over time in both groups, whereas osteocalcin decreased at 12 months only after subtotal parathyroidectomy. The bone resorption biomarker C–terminal telopeptide was significantly reduced only after subtotal parathyroidectomy. Also, calcidiol levels increased over time only after subtotal parathyroidectomy, because the majority of patients received oral calcium and vitamin D supplementation early after surgery to prevent hypocalcemia caused by hungry bone syndrome. Nevertheless, in the cinacalcet group, mean levels of calcidiol were >50 nmol/L during all of the study follow-up. Interestingly, only subtotal parathyroidectomy was associated with a significant improvement in BMD at 12 months, in particular in the femoral neck as shown in Table 3.

Evolution of eGFR and proteinuria is shown in Table 2. There was some degree of eGFR loss in both groups without increase in proteinuria. During the 12-month follow-up, eGFR decline was 9 ml/min in the cinacalcet group (P=0.01) and 4 ml/min in the parathyroidectomy group (P=0.10) (Figure 3). However, no statistically significant differences were observed in GFR between both groups.

We performed assessment of vascular calcification by computed tomography (CT) at baseline and 6 and 12 months.

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

Variable	Cinacalcet				Subtotal 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 for calcidiol, nmol/L	51±24	57±21	59±21	53±15	41±14	90±32[b]	79±31[b]	70±30[b]
Bone resorption biomarker								
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]
Bone formation biomarkers								
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]
Renal function								
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
Vascular calcification								
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

25(OH)D₃, 25-hydroxy vitamin D (calcidiol); μKat, katal; —, not done as per protocol.
[a]P<0.05 versus baseline in the cinacalcet group.
[b]P<0.05 versus baseline in the subtotal parathyroidectomy group.

No differences were observed between groups at baseline, and calcification score remained unchanged during follow-up (Figure 4, Table 2).

Safety

One patient in the cinacalcet group discontinued the drug because of digestive intolerance and severe xerostomia. Adverse events in the cinacalcet arm were diarrhea ($n=2$), nausea/vomiting ($n=2$), edema ($n=2$), urinary tract infection ($n=2$), and renal dysfunction ($n=2$). Adverse events in the 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 two patients requiring hospitalization because of severe hypocalcemia after parathyroidectomy, whereas one patient in the cinacalcet group was admitted to the hospital because of severe diarrhea. During the course of the study, no acute rejection episodes, cytomegalovirus, or BK virus infections were observed. All patients were alive with a functioning graft at the end of follow-up.

Economic Study

The cost of both therapies for the Catalan Health Service was calculated. In the parathyroidectomy group, we included parathyroid gland scintigraphy; neck ultrasound; preoperative assessment; surgical, anesthetic, and hospitalization costs; pathologic report; rehospitalization cost; and 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 euros in the parathyroidectomy group and 3258 euros in the cinacalcet group (12% higher in parathyroidectomy). The 1-year cost of cinacalcet drug was 3003 euros per patient (1-month cost per patient was 250 euros). Therefore, if cinacalcet treatment duration reached at least 14 months, subtotal parathyroidectomy would be considered superior in terms of cost-effectiveness.

Table 3. BMD at baseline and month 12 with percentage changes of BMD calculated in the study groups

Variable	Subtotal Parathyroidectomy	Cinacalcet	P Value
BMD baseline, g/cm^2			
Femoral neck	0.819±0.164	0.723±0.089	0.12
Lumbar spine	0.993±0.227	0.904±0.106	0.25
Distal 1/3 radius	0.613±0.097	0.661±0.116	0.30
BMD month 12, g/cm^2		Article I.	
Femoral neck	0.846±0.149	0.700±0.081	0.01
Lumbar spine	1.015±0.213	0.896±0.109	0.11
Distal 1/3 radius	0.630±0.086	0.658±0.114	0.52
Change at month 12, %			
Femoral neck	+3.8±6.1	−3.0±5.1	0.01
Lumbar spine	+2.7±7.8	−0.9±4.7	0.21
Distal 1/3 radius	+3.3±6.6	−0.4±2.6	0.10

Data is displayed as means±standard deviation.

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 subtotal parathyroidectomy and ≤70% with cinacalcet achieved normocalcemia. Moreover, the reduction of iPTH was greater in the parathyroidectomy group than in the cinacalcet group. Accordingly, only subtotal parathyroidectomy was associated with a significant improvement in BMD in femoral neck.

A recent clinical trial showed that cinacalcet compared with placebo is a highly effective treatment option for correcting serum calcium levels among this population.[20] Our results in the cinacalcet arm were similar, because 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. It is postulated in experimental studies that cinacalcet increases calcitonin levels and thus, decreases blood calcium levels[21]; this could be explained by the activation of sensitive calcium receptors present in the C cells of the thyroid gland. This theory could explain why, in many studies involving cinacalcet treatment of hypercalcemia in secondary hyperparathyroidism, serum calcium levels significantly decrease without a parallel decrease in PTH. In fact, the high level of the bone turnover biomarker C–terminal telopeptide throughout the study in the cinacalcet group suggests that persistence of hyperparathyroidism could be the potential explanation for the lack of improvement in BMD in patients treated with this drug.[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 adynamic bone disease.[22] Adynamic bone disease can be indirectly assessed by bone turnover biomarkers.[23] Among them, alkaline phosphatase is the best. In this regard, alkaline phosphatase levels, although with some decline, were maintained above normal range. In theory, normal range alkaline phosphatase makes the presence of adynamic bone disease unlikely. Moreover, the performance of osteocalcin was similar. Therefore, it seems that, at least after 1-year follow-up, the assessment of bone synthesis biomarkers does not suggest the presence of adynamic bone disease in cinacalcet and parathyroidectomy groups. Instead, in our study, subtotal parathyroidectomy was associated with improvement in BMD 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
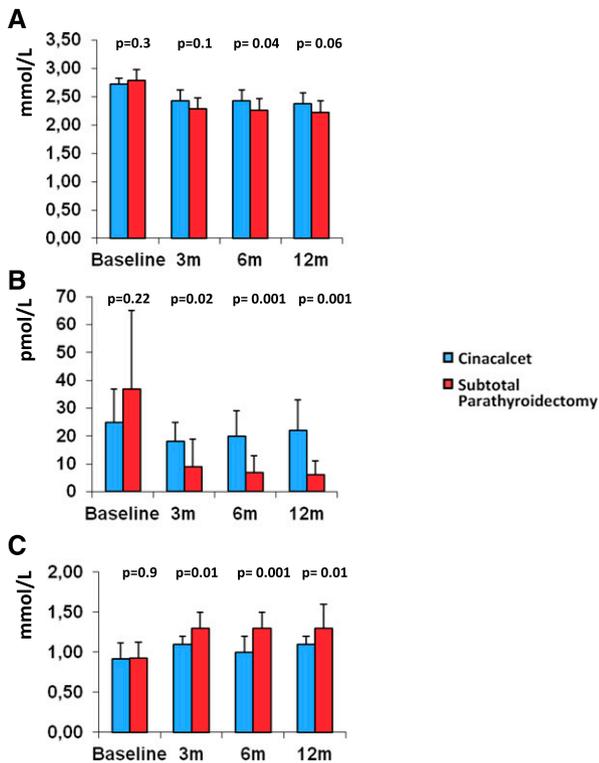
Figure 2. Subtotal parathyroidectomy was associated with a higher proportion of patients achieving normocalcemia and iPTH normalization. (A) Serum calcium, (B) iPTH, and (C) phosphate evolution in the cinacalcet and subtotal parathyroidectomy groups. Both treatments was associated with correction of calcium and phosphate, although the reduction of iPTH was greater in the parathyroidectomy group than in the cinacalcet group.

associated with hungry bone syndrome, which was confirmed by a significant increase in calcidiol levels.[14,24] Additional studies with cinacalcet combined with vitamin D in which iPTH correction would be the primary end point are needed to ask this question properly.

Vascular calcification is an important complication in patients with secondary hyperparathyroidism.[25] We observed similar results in cinacalcet and parathyroidectomy groups, and both treatments were associated with no progression in vascular calcification. Subtotal parathyroidectomy was not associated with regression of vascular calcification, although nearly full correction of serum calcium and iPTH was achieved. 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 CKDs.

There are some previous studies suggesting that both cinacalcet and parathyroidectomy are associated with a decrease in renal function.[17,26] However, this effect was not observed in the previous cinacalcet clinical trial,[20] and long–term graft outcome was not affected by parathyroidectomy.[26] A renal hemodynamic mechanism was suggested, because iPTH

has a known positive regulatory effect on renal perfusion and GFR that can be abrogated by intervention therapies.[27] In our study, a 12-month GFR decline was observed in both groups, although it was greater in the cinacalcet group than in the parathyroidectomy group. There were no rejection episodes to explain this finding. The gastrointestinal adverse events observed in some patients treated with cinacalcet could be associated with hypovolemia and renal dysfunction. Previous studies showed association between high iPTH levels, kidney allograft interstitial calcification, and loss of renal function, providing a rationale to our finding.[28] 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,[29] being a limitation to increasing the cinacalcet dose sufficiently to achieve serum calcium correction in some patients. Complications of subtotal parathyroidectomy depend on both surgical experience and the procedure itself.[16] A recent study reviewed early outcomes of 4435 patients on dialysis who underwent parathyroidectomy[30] and reported 2% mortality and 23.8% rehospitalization 30 days after discharge. Nevertheless, other studies have shown that successful parathyroidectomy may reduce the risk for all-cause and cardiovascular mortality in patients on dialysis.[31,32] To minimize surgical bias, the same surgical team performed all parathyroid surgeries. 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 the cinacalcet group. As expected, the main complication after subtotal parathyroidectomy was hypocalcemia, some of which was related to oral intolerance caused by high calcium doses and some of which was related to transient dysfonia caused by recurrent laryngeal nerve mild surgical traumatism.
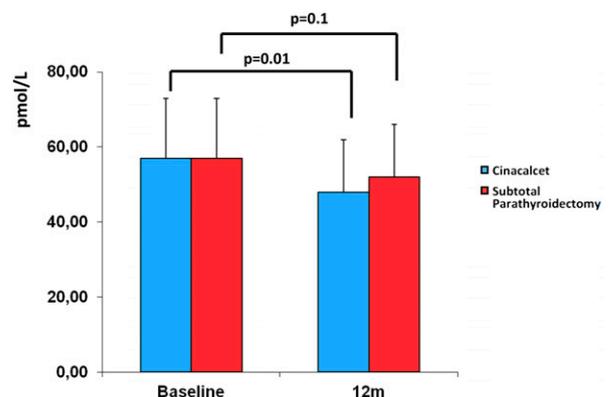

Figure 3. There was some degree of eGFR loss in the cinacalcet and subtotal parathyroidectomy groups. eGFR at baseline and month 12 in the cinacalcet and subtotal parathyroidectomy groups. Decline in renal function was greater in the cinacalcet group than in the parathyroidectomy group.
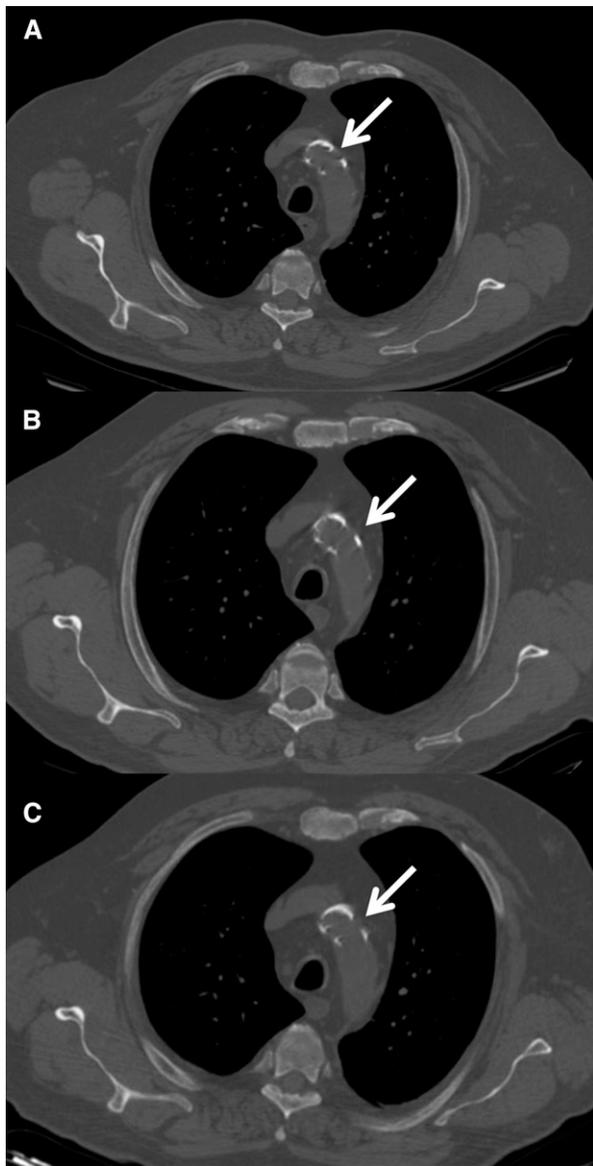
Figure 4. Vascular calcification score remained unchanged in the cinacalcet and subtotal parathyroidectomy groups. A representative patient to assess changes in vascular calcification. Unenhanced CT scan at the level of the aortic arch in the same patient at (A) baseline, (B) 6 months, and (C) 12 months. Multiple plaques are seen (arrows), with no variation during the follow-up. Calcification value at this level was three at all three time points.

There is a paucity of data regarding the optimal management of tertiary hyperparathyroidism.[22] A cost-utility analysis has been reported comparing subtotal parathyroidectomy with cinacalcet in patients on dialysis with severe hyperparathyroidism.[33] 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, because the 1-year economic cost associated with both treatments is similar, suggesting that subtotal parathyroidectomy is more cost effective in the long term. However, this

estimate applies in Spain and should be considered cautiously in other countries.

Our study has some limitations. First, follow-up is probably too short to provide relevant information about fracture risk, vascular calcification, and recurrence of hyperparathyroidism after subtotal parathyroidectomy. Second, cinacalcet dosage was adjusted to achieve normocalcemia without taking into account iPTH reduction. Third, the fact that the same surgeon performed all parathyroid surgeries could be a limitation to making a general recommendation. Fourth, in the absence of bone biopsies, it may be difficult to ascertain bone turnover in patients with renal transplants.[34] Nevertheless, taking into account that our results in the cinacalcet arm are similar to those previously reported[20] and that extended minimally invasive subtotal parathyroidectomy is a feasible approach,[35] our results could reasonably be reproduced in a big clinical trial.

In conclusion, both cinacalcet and subtotal parathyroidectomy are effective to control hypercalcemia caused by persistent hyperparathyroidism after kidney transplantation. However, subtotal parathyroidectomy is superior to cinacalcet in terms of the proportion of patients achieving calcium (100% versus 67%; $P=0.04$) and iPTH (67% versus 0%; $P<0.001$) normalization, increase in BMD in the femoral neck (+3.8% versus -3%; $P=0.01$), and cost-effectiveness.

CONCISE METHODS

Study Population

This was an investigator–promoted, prospective, multicenter, open–label, and randomized study performed in renal allograft recipients with hypercalcemia caused by post–transplant persistent hyperparathyroidism. The study was approved by The Spanish Drug Agency (EudraCT 2008–007017–76) and registered at ClinicalTrials.gov (NCT01178450).

Inclusion criteria were defined as follows: a functioning renal graft with an eGFR≥30 ml/min, at least 6 months after kidney transplantation, serum iPTH level ≥15 pmol/L, corrected total serum calcium level ≥2.63 mmol/L, and serum phosphate level ≤1.2 mmol/L. Before inclusion, patients were managed according to clinical guidelines and local clinical practice. Subjects were required to have a 16-week washout if they received cinacalcet. Use of vitamin D analogs and/or biphosphonates was not allowed during the study. Patients who did not meet the inclusion criteria or had a contraindication for 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 the screening period, a complete laboratory assessment was performed (including iPTH and calcium and phosphate serum levels) to verify that patients met inclusion/exclusion criteria. At baseline, a parathyroid gammagraphy was performed to identify ectopic parathyroid tissue. Women of child-bearing potential were tested for pregnancy at the screening visit and informed to avoid pregnancy during the study. Patients who did not meet inclusion/exclusion criteria after the screening period

were considered as screening failures and were 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 patients by the same surgeon (P.M.) at Bellvitge Hospital. Briefly, the neck was explored bilaterally, and all parathyroid glands were identified and tissue was removed, leaving a remnant equivalent to one normal gland in size (50 mg). A perioperatively pathologic assessment was performed in all patients. A systematic transcervical thymectomy was also added to prevent persistent disease secondary to a fifth gland that could be present in ≤15% of patients. Intraoperative iPTH assessment was measured at baseline and 10 minutes after subtotal parathyroidectomy.

Patients assigned to the cinacalcet group started with 30 mg/d, and then, the dose was adjusted to achieve the objective of normocalcemia. Patients assigned to the subtotal 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 the cinacalcet treatment or parathyroidectomy. Study visits were performed at baseline and 3, 6, and 12 months.

Primary and Secondary Efficacy End Points

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

Serious and nonserious adverse events were monitored throughout the length of the study and reported accordingly. BMD was evaluated at baseline and month 12 at the 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 and 6 and 12 months and centralized at Bellvitge Hospital. Patients underwent thoracic, abdominal, and pelvis unenhanced CT scans. The images obtained were assessed for calcification detection and scoring by a radiologist (R.M.) who was blinded to therapy and timing of the CT scans. Imaging was performed using a 16– or 64–slice CT system (General Electric); 1.25-mm slices were obtained from the thorax, abdomen, and pelvis with posterior 0.625-mm-thick reconstructions. All of 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 supra-aortic 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, and 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 zero was given for the absence of calcification deposit, one was given for presence of plaques, and two was given if more than four plaques were detected. An extra point was given when the plaque occupied >50% of the arterial circumference, and an extra two points were given when it was covering the entire circumference. Finally, one extra

point was assigned when the thickness of the plaque was >4 mm in any of the deposits detected. On the basis of this system, the final score could be between 0 and 80. Stability or progression of calcifications deposits was achieved comparing the three CT scans performed for each patient.

Statistical Analyses

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-squared test. This assumed a response rate for normocalcemia of 65% in cinacalcet and 95% in subtotal parathyroidectomy. An intention to treat analysis was performed. Differences in the categorical variables between both groups were calculated by means of the chi-squared test or the Fisher exact test. The differences in the quantitative variables, including the main variable between groups, were calculated by means of the t test or the Mann–Whitney U test. A P value <0.05 was considered significant for all tests. Results were depicted as means ± SDs.

DISCLOSURES

None.

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