Renal function in patients treated with cinacalcet for persistent hyperparathyroidism after kidney transplantation

Henschkowski, J ; Bischoff-Ferrari, H A ; Wüthrich, R P ; Serra, A L

DOI: https://doi.org/10.1159/000323902

Renal function in patients treated with cinacalcet for persistent hyperparathyroidism after kidney transplantation.

Jana Henschkowski[1] Heike A. Bischoff-Ferrari[1], Rudolf P. Wüthrich[2] and Andreas L. Serra[2]

[1]Centre on Aging and Mobility, University of Zürich, CH-8091 Zürich, Switzerland

[2]Division of Nephrology, University Hospital, CH-8091 Zürich, Switzerland

Running headline: cinacalcet and kidney function

Word count abstract: 200

Word count body: 2055

Address correspondence to:

Andreas L. Serra, M.D.

Division of Nephrology

University Hospital

Rämistrasse 100

8091 Zürich

Switzerland

Tel. +41 44 255 33 84

Fax. +41 44 255 45 93

E-Mail andreas.serra@usz.ch

ABSTRACT

Background and aim

Cinacalcet effectively reduces calcium in patients with persistent hyperparathyroidism (HPT) after kidney transplantation. We aimed to assess the association of cinacalcet with decrease in renal function based on a meta-analysis of observational studies in kidney transplant patients with persistent HPT.

Method

Meta-Analysis of observational studies, no randomized controlled studies were available. We calculated the mean difference between renal function before cinacalcet and at 3 months on cinacalcet treatment for each study. Pooled analyses are based on random effects models.

Results

Pooling the studies on kidney transplant patients with persistent HPT (8 studies, n=115), we found a significant reduction in renal function ($p = 0.008$). The effect size was 5 μmol/l ($p< 0.0001$) when pooling the 7 studies where serum creatinine levels were reported. Meta-regression analysis revealed that there was an association between renal function and the amount of calcium reduction under treatment with cinacalcet. A higher delta change in serum calcium levels was associated with a decrease in renal function at 3 months of cinacalcet treatment.

Conclusion

Cinacalcet treatment was associated with a decline of renal function in kidney transplant recipients with persistent HPT. Our meta-analysis underscores the need for frequent monitoring of creatinine and calcium levels during cinacalcet treatment.

INTRODUCTION

Cinacalcet is a calcimimetic drug that increases the sensitivity of the calcium-sensing receptor (CaSR) to extracellular calcium, which leads to a decrease of parathyroid hormone secretion and subsequently to lower serum calcium concentrations [1, 2]. The agent has been approved for treatment of dialysis patients with secondary hyperparathyroidism (HPT), and has substantially expanded the therapeutic options in the management of HPT.

Persistent HPT with subsequent hypercalcemia after renal transplantation occurs frequently [3, 4] and is a risk factor for bone disease, promote vascular and tubulointerstitial calcifications and has been associated with decreased graft survival and enhanced post-transplant cardiovascular morbidity and mortality [5-8]. Effective control of persistent HPT is an important therapeutic goal after renal transplantation but poses a particular challenge. As active vitamin D treatment and calcium supplementation are contraindicated because they promote hypercalcemia, parathyroidectomy often remains the only therapeutic option. Encouraged by the success of cinacalcet to control biochemical parameters of HPT in dialysis patients [9], several studies including our own have shown that treatment with cinacalcet effectively corrects hypercalcemia in these patients [10-19]. Given the efficacy of cinacalcet to control hypercalcemia and the limited therapeutic options in these patients, cinacalcet has been off-label used in many transplant clinics. Hence, the awareness of a potential harmful effect of cinacalcet on renal function is of particular importance.

Yet recently, investigators reported conflicting results of the effect of cinacalcet on renal function as well as cases of acute kidney failure after the initiation of cinacalcet in patients with intractable primary hyperparathyroidism [20]. However, the effect of cinacalcet on renal function was not systematically investigated. First, since cinacalcet treatment was established mainly in dialysis patients, a renal-specific adverse effect of cinacalcet would not have been detectable. Notably, renal function was not reported in phase III studies of patients with primary HPT [21]. Second, the planed phase III studies in kidney transplant patients with hypercalcemia due to persistent HPT is designed to test cinacalcet profound effect on parathyroid hormone (PTH) and serum calcium and thus smaller effects on renal function will maybe not found.

The primary goal of our analyses was to determine the short term effect of cinacalcet on renal function in renal transplant patients with persistent hyperparathyroidism by performing a systematic review of the literature and meta-analysis of peer-reviewed reports.

METHODS

Search Strategy and Data Extraction

We conducted a systematic search for relevant English and non-English publications using Medline (Ovid, Pubmed) for the period January 1990 to August 2009 and EMBASE for January 1990 to August 2009. We searched reference lists and abstracts presented at the American Society of Nephrology from 2002 to 2008. Search terms included "cinacalcet" or "mimpara" or "sensipar" or "calcimimetic*" or "R586". Eligibility and exclusion criteria were pre-specified. No consensus procedure was necessary because identical data were extracted by the two reviewers (JH, ALS). Eligibility and exclusion criteria, as well as subgroup variables for potential sources of heterogeneity and their priority were pre-specified.

Eligible Studies

We included trials that studied oral cinacalcet in adult kidney transplant patients with the diagnosis of hyperparathyroidism (HPT) with a minimum follow up of at least 1 month. To be included in the primary analysis we required that renal function was assessed at baseline and at follow up (>1 months and ≤3 months). Eligible studies that did not meet the criteria for the primary analysis were included in a sensitivity analysis including studies with different follow-up times among study participants.

Ineligible Studies

We excluded case reports, reviews, letters, editorials, and non peer-reviewed publications. We also excluded animal investigations, phase I studies, studies in patients

on dialysis, studies on patients with primary or secondary HPT, studies on lithium induced HPT and studies on patients with hyperparathyreoid carcinoma.

Definitions

Our primary outcome measure was the mean difference of renal function between baseline and follow-up for each study assessed by pre-/post-treatment serum creatinine or estimated or measured GFR.

Studies identified for Primary Analysis

A total of 8 separate studies were identified in patients with persistent HPT after kidney transplantation (**Table 1)** [12, 14, 17, 18, 22-25].

Studies identified for Sensitivity Analysis

In sensitivity analyses, we examined the effect of cinacalcet on renal function when including studies meeting less stringent quality criteria. 3 studies were identified for the sensitivity analysis on persistent HPT after kidney transplantation [10, 26, 27]. Two studies were excluded from the primary analysis for their high variability in follow-up time among patients (3-18 months) and one for not peer reviewed.

Statistical Analysis

The primary outcome of the pooled analysis was the mean difference in renal function before cinacalcet initiation and at follow-up of each study. As renal function was assessed by serum creatinine in micromole per liter or glomerular filtration rate (GFR) in milliliter per minute we calculated the pooled random-effects mean difference and 95% CI between pre-treatment and post-treatment values divided by the pooled standard

deviation (Hedges's *g*). The correlation factor pre-/post-treatment serum creatinine was calculated from raw data (r=0.95, n=22) from 2 studies [14, 22] and was used as an estimate for the others. Results from all studies were then pooled using random effects models.

Heterogeneity among studies was explored using the Q-statistic as a test (considered significant for p-values <0.10) and I^2 that ranges between 0% and 100% with lower values representing less heterogeneity. Predefined subgroup analyses were performed for mean difference in serum calcium levels using visual inspection, and random-effect meta-regression analysis.

To assess potential publication bias, we used Begg's and the Egger's tests and Begg's funnel plot; no evidence of bias was seen. Statistical analysis was performed by using comprehensive meta-analysis (CMA) version 2.

RESULTS

A total of 1157 articles were found in our initial search, 1095 of which could be excluded by screening the titles and abstracts (Figure 1). A further 51 articles were excluded because they did not meet the inclusion criteria. 4 studies were excluded due to duplicates. Table 1 displays the characteristics of the 8 studies that met our inclusion criteria and of 3 studies that were included in the sensitivity analysis. All studies were performed to test the efficacy of cinacalcet on PTH and calcium reduction.

Primary analyses of studies on persistent HPT after kidney transplantation

8 studies involved a total of 115 patients (mean age 53.6 years) with stable allograft function (mean time after transplantation 37.8 months, range 6 to 74 months) [12, 14, 17, 18, 22-25]. Mean follow up time was 5.7 months (range 1 to 12 months). Cinacalcet was given in a start-dose of 30 mg/d in 7 studies and 60 mg/d in 1 study. At end of follow-up mean dose was 47.25 mg/d (Table 1).

Figure 2 shows the forest plot for the mean difference in renal function (as Hedges's *g*) under treatment with cinacalcet in renal allograft patients with persistent HPT. Pooling the 8 studies there was a significant association between cinacalcet treatment and decline of renal function (mean difference of Hedges's *g* -0.188 (95% CI, -0.327 to -0.048), p=0.008). Pooling 7 studies reporting serum creatinine levels, mean serum creatinine increased by 5 μmol/L (95% CI, 2.4 to 7.5, p<0.0001). There was no significant heterogeneity in results among studies (Q-test: p-value = 0.16, I^2 33.6%) (Table 2). In 6 out of the 8 studies from our primary analysis concomitant treatment was unchanged. When pooling these studies, the association between cinacalcet treatment and decline of

renal function remained significant (mean difference of Hedges's *g* -0.180 (95% CI, -0.310 to -0.051, p=0.006) and no significant heterogeneity in results among studies (Q-test: p-value = 0.34, I^2 11.3%) was detected.

Subgroup-analysis

Random effects meta-regression analysis revealed a significant association between change in serum calcium levels and decline in renal function (**Figure 3**, $\beta = -2.05$, p=0.004). For subgroup analysis studies were dichotomized into studies with higher and lower serum calcium change based on the median. In the low calcium change group [12, 17, 23, 25], the pooled mean difference of Hedges's *g* was -0.018 (95% CI, -0.186 to 0.150) with lower calcium reduction compared to -0.315 (95% CI, -0.46 to -0.167, p value < 0.001) for trials with higher calcium reduction [14, 18, 22, 24]. Pooling 3 studies reporting serum creatinine and low delta calcium, serum creatinine remained unchanged (0.3 μmol/L, 95% CI; -9.0 to 9.6, p=0.95) and in the high delta calcium group, serum creatinine increased by 5.6 μmol/L (95% CI, 2.5 to 8.6, p<0.0001).

Sensitivity analysis

After adding 3 studies that did not meet our criteria for the primary analysis (**Table 1)** to the 8 trial of the primary analysis (total n = 162 individuals), the pooled mean difference of Hedges's *g* was -0.100 (95% CI, -0.193 to -0.007, p-value 0.035). However, variation among the 11 trials was larger than expected (Q-test: p = 0.043, I^2 47%) suggesting that the follow-up time point introduces heterogeneity.

DISCUSSION

Based on small observational studies, we found an association between cinacalcet treatment and decline in renal function among renal allograft recipients with persistent HPT. The decline of renal function was related to the degree of calcium reduction during follow-up of 1 to 3 months.

We found a small but significant (P=0.008) decline in renal function observed in our meta-analysis. In 5 out of 8 studies eligible for primary analysis, renal function tended to decline. After adding 3 studies (total n=162 patients) that did not meet our criteria for primary analysis, the pooled mean difference remained significant. Pooling 7 studies reporting serum creatinine levels, the mean serum creatinine increased by 5 µmol/L. The difference was highly significant (P<0.0001) although the absolute difference appears to be small. The serum creatinine high inter-subject variability may have diminished the true difference in our study and thus we can not exclude that our meta-analysis underestimated the effect. Indeed, we prospectively measured serum creatinine and estimated GFR values in 10 kidney allograft recipients with persistent hyperparathyroidism after cinacalcet treatment start, cinacalcet withdrawal and re-exposure. Mean serum creatinine values increased by 12 µmol/l (95% CI 40 to -16) and 11 µmol/l (95% CI 40 to -16) and estimated GFR (MDRD) decreased by 6 ml/min (95% CI -20 to 8) and 6 ml/min (95% CI -21 to 8) after cinacalcet initiation at week 0 and cinacalcet re-exposure at week 30, respectively (Figure 4).

Our observation that cinacalcet initiation, withdrawal and re-exposure changed serum creatinine fast and reversible as well as the finding of two studies reporting a restoration

of renal function after cessation of cinacalcet [14, 19], suggests a hemodynamic rather than structural effects. The decline in renal function observed in our meta-analysis correlated very well with the delta serum calcium but not with delta PTH. This differential finding can be explained by unchanged pre-dose PTH levels but constantly reduced serum calcium levels over 24 hours in cinacalcet treated kidney transplant patients. Cinacalcet has the unique ability to suppress serum calcium persistently over 24 hours, whereas PTH levels are only transiently reduced with a nadir 2-6 hrs after dosing [22]. Zoledronic acid is a bisphosphonate that lowers serum calcium levels to same magnitude compared to cinacalcet. In line with our meta-regression result, impairment of creatinine clearance was seen more often in subjects developing hypocalcemia than in those remaining normocalcemic [28] suggesting a common pathophysiologial mechanism.

The results of our study have to be interpreted in the context of the available data and its quality, in particular, the limited information on changes of concomitant therapy and the absence of an untreated control. However, pooling 6 prospective studies reporting unchanged concomitant treatment, cinacalcet treatment was associated with a decrease of renal function. In total, only 8 studies met the inclusion criteria and they were small observational single centre studies in which renal function was not a predefined primary outcome measurement. It is debatable whether results of such observational studies should be pooled. However, drug safety call for formal meta-analysis as adverse effects are rare and unlikely to be found in studies designed for efficacy endpoint. It is also well accepted that the quality of a meta-analysis depends largely on the quality of the rough

data. The remarkable low heterogeneity in our study indicates robustness of the meta-analysis and gives support to our hypothesis of a renal function decline in relation to the decrease of serum calcium which is in line with two previous reports of renal function restoration after cinacalcet withdrawal [14, 19]. Information on measured glomerular filtration rate was not available. However, change of renal allograft function within an interval of 3 months can reliably be assessed by serial measurements of serum creatinine levels in stable long-term kidney transplant patients.

In summary, our results suggest that cinacalcet has a small but significant effect on renal function short-time after cinacalcet initiation in kidney transplant patients with persistent HPT. Our meta-analysis underscores the need for frequent monitoring of creatinine and calcium levels during cinacalcet treatment.

References

1 Nemeth EF, Steffey ME, Hammerland LG, Hung BC, Van Wagenen BC, DelMar EG, Balandrin MF: Calcimimetics with potent and selective activity on the parathyroid calcium receptor. Proc Natl Acad Sci U S A 1998;95:4040-4045.

2 Brown EM, Hebert SC: Calcium-receptor-regulated parathyroid and renal function. Bone 1997;20:303-309.

3 Lobo PI, Cortez MS, Stevenson W, Pruett TL: Normocalcemic hyperparathyroidism associated with relatively low 1,25 vitamin d levels post-renal transplant can be successfully treated with oral calcitriol. Clin Transplant 1995;9:277-281.

4 Reinhardt W, Bartelworth H, Jockenhovel F, Schmidt-Gayk H, Witzke O, Wagner K, Heemann UW, Reinwein D, Philipp T, Mann K: Sequential changes of biochemical bone parameters after kidney transplantation. Nephrol Dial Transplant 1998;13:436-442.

5 Julian BA, Quarles LD, Niemann KM: Musculoskeletal complications after renal transplantation: Pathogenesis and treatment. Am J Kidney Dis 1992;19:99-120.

6 Hernandez D, Rufino M, Bartolomei S, Gonzalez-Rinne A, Lorenzo V, Cobo M, Torres A: Clinical impact of preexisting vascular calcifications on mortality after renal transplantation. Kidney Int 2005;67:2015-2020.

7 Gwinner W, Suppa S, Mengel M, Hoy L, Kreipe HH, Haller H, Schwarz A: Early calcification of renal allografts detected by protocol biopsies: Causes and clinical implications. Am J Transplant 2005;5:1934-1941.

8 Schwarz A, Rustien G, Merkel S, Radermacher J, Haller H: Decreased renal transplant function after parathyroidectomy. Nephrol Dial Transplant 2007;22:584-591.

9 Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drueke TB, Goodman WG: Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;350:1516-1525.

10 Apostolou T, Damianou L, Kotsiev V, Drakopoulos S, Hadjiconstantinou V: Treatment of severe hypercalcemia due to refractory hyperparathyroidism in renal transplant patients with the calcimimetic agent cinacalcet. Clin Nephrol 2006;65:374-377.

11 Apostolou T, Kollia K, Damianou L, Kaitsioti H, Kotsiev V, Dracopoulos S, Vougas V, Hadjiconstantinou V: Hypercalcemia due to resistant hyperparathyroidism in renal transplant patients treated with the calcimimetic agent cinacalcet. Transplant Proc 2006;38:3514-3516.

12 El-Amm JM, Doshi MD, Singh A, Migdal S, Morawski K, Sternbauer D, Cincotta E, West MS, Losanoff JE, Gruber SA: Preliminary experience with cinacalcet use in persistent secondary hyperparathyroidism after kidney transplantation. Transplantation 2007;83:546-549.

13 Leca N, Laftavi M, Gundroo A, Kohli R, Min I, Karam J, Sridhar N, Blessios G, Venuto R, Pankewycz O: Early and severe hyperparathyroidism associated with hypercalcemia after renal transplant treated with cinacalcet. Am J Transplant 2006;6:2391-2395.

14 Serra AL, Savoca R, Huber AR, Hepp U, Delsignore A, Hersberger M, Wuthrich RP: Effective control of persistent hyperparathyroidism with cinacalcet in renal allograft recipients. Nephrol Dial Transplant 2007;22:577-583.
15 Serra AL, Schwarz AA, Wick FH, Marti HP, Wuthrich RP: Successful treatment of hypercalcemia with cinacalcet in renal transplant recipients with persistent hyperparathyroidism. Nephrol Dial Transplant 2005;20:1315-1319.
16 Srinivas TR, Schold JD, Womer KL, Kaplan B, Howard RJ, Bucci CM, Meier-Kriesche H-U: Improvement in hypercalcemia with cinacalcet after kidney transplantation. Clin J Am Soc Nephrol 2006;1:323-326.
17 Szwarc I, Argiles A, Garrigue V, Delmas S, Chong G, Deleuze S, Mourad G: Cinacalcet chloride is efficient and safe in renal transplant recipients with posttransplant hyperparathyroidism. Transplantation 2006;82:675-680.
18 Kruse AE, Eisenberger U, Frey FJ, Mohaupt MG: The calcimimetic cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism. Nephrol Dial Transplant 2005;20:1311-1314.
19 Kruse AE, Eisenberger U, Frey FJ, Mohaupt MG: Effect of cinacalcet cessation in renal transplant recipients with persistent hyperparathyroidism. Nephrol Dial Transplant 2007;22:2362-2365.
20 Marcocci C, Chanson P, Shoback D, Bilezikian J, Fernandez-Cruz L, Orgiazzi J, Henzen C, Cheng S, Sterling LR, Lu J, Peacock M: Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab 2009;94:2766-2772.
21 Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D: Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 2005;90:135-141.
22 Serra AL, Braun SC, Starke A, Savoca R, Hersberger M, Russmann S, Corti N, Wuthrich RP: Pharmacokinetics and pharmacodynamics of cinacalcet in patients with hyperparathyroidism after renal transplantation. Am J Transplant 2008;8:803-810.
23 Kamar N, Gennero I, Spataru L, Esposito L, Guitard J, Lavayssiere L, Cointault O, Gandia P, Durand D, Rostaing L: Pharmacodynamic effects of cinacalcet after kidney transplantation: Once- versus twice-daily dose. Nephrol Dial Transplant 2008;23:3720-3726.
24 Borchhardt KA, Heinzl H, Mayerwoger E, Horl WH, Haas M, Sunder-Plassmann G: Cinacalcet increases calcium excretion in hypercalcemic hyperparathyroidism after kidney transplantation. Transplantation 2008;86:919-924.
25 Bergua C, Torregrosa JV, Fuster D, Gutierrez-Dalmau A, Oppenheimer F, Campistol JM: Effect of cinacalcet on hypercalcemia and bone mineral density in renal transplanted patients with secondary hyperparathyroidism. Transplantation 2008;86:413-417.
26 Srinivas TR, Schold JD, Womer KL, Kaplan B, Howard RJ, Bucci CM, Meier-Kriesche HU: Improvement in hypercalcemia with cinacalcet after kidney transplantation. Clin J Am Soc Nephrol 2006;1:323-326.
27 Lopez V, Toledo R, Sola E, Gutierrez C, Sujan S, Rodriguez MA, Cabello M, Burgos D, Gonzalez Molina M, Hernandez D: Treatment with cinacalcet in 29 kidney transplant patients with persistent hyperparathyroidism. Transplant Proc 2009;41:2394-2395.

28 Chennuru S, Koduri J, Baumann MA: Risk factors for symptomatic hypocalcaemia complicating treatment with zoledronic acid. Intern Med J 2008;38:635-637.

Disclosure

The author(s) declare that they have no competing interests.

Acknowledgements

The authors thank Harald Schneider for valuable comments.

.

Table 1: Studies that assessed renal function before cinacalcet treatment and at follow-up

Study, year	Study design	FU; month	Study patients enrolled (n male)	Age (SD), years	BL serum creatinine (SD) µmol/L	BL GFR (SD) ml/min	BL serum calcium, mmol/L	BL and final cinacalcet dose, mg/day
Kidney transplantation 3° HPT, included in primary analysis								
El-Amm, 2007 [12]	Cohort retrospective	6	18 (8)	45 (13)	159 (97)	59	2.54 (0.22)	30 (60)
Serra, 2007 [14]	Cohort, prospective	4	12 (6)	59 (2)	116 (30)	56 (16.6)	2.73 (0.14)	30 (34)
Serra, 2008 [22]	Cohort prospective	1	10 (6)	59 (range 47-70)	134 (35)	49.7 (18.3)	2.55 (0.19)	30 (60)
Bergua, 2008 [25]	Cohort prospective	12	9 (1)	61.8 (5.8)	140 (30)	51.4 (10.5)	2.92 (0.1)	30 (45)
Borchhardt, 2008 [24]	Cohort, prospective	1.5	32 (22)	56 (range 21-71)	138 (15)	48 (range 17-90)	2.77 (range 2.71-2.80)	30 (30)
Szwarc, 2006 [17]	Cohort prospective	6	9 (9)	52 (11)	NA	49.8 (18.6)	2.75 (0.15)	30 (55)
Kruse, 2005 [18]	Cohort retrospective	3	14 (7)	23-65 (range)	140 (56)	NA	2.72 (0.11)	30 (30)
Kamar, 2008 [23]	Cohort, prospective	12	11 (6)	50.5 (range 29-65)	119 (48)	56 (17)	2.68 (0.17)	60 (60)
Kidney transplantation 3° HPT, included in sensitivity analysis								
Srinivas, 2006 [16]	Cohort, retrospective	3-18	11 (6)	48.5 (range 22-64)	134 (42.1)	NA	2.71 (0.1)	30 (NA)
Apostolou, 2006 [10]	Cohort, retrospective	3- 18	7 (4)	56 (11)	140 (18)	NA	1.89 (0.15)	30 (NA)
Lopez, 2009 [27]	Cohort prospective	13	29 (14)	56 (11)	NA	45 (16)	2.78 (0.2)	30 (60)

Table 2

HPT type, study, year	**Change in renal function, mean (95% CI)**	**p-value (Q-test), I^2**
Persistent HPT	*Estimated GFR (ml/min)*	
Szwarc, 2006 [17]	-0.9 (-9.9 to 8.1)	
Persistent HPT	*Serum creatinine (µmol/L)*	
Kruse, 2005 [18]	-8.0 (-13.2 to -2.8)	
El-Amm, 2007 [12]	0.0 (-26.9 to 26.9)	
Serra, 2007 [14]	-12.0 (-24.1 to 0.1)	
Bergua, 2008 [25]	4.0 (-7.9 to 15.9)	
Borchhardt, 2008 [24]	-3.0 (-6.3 to 0.3)	
Kamar, 2008 [23]	-8.0 (-25.9 to 9.9)	
Serra, 2008 [22]	-6.0 (-10.9 to -1.1)	
Pooled (random)	**-5 (-7.5 to – 2.4), p<0.0001**	0.2, 34%
Persistent HPT Subgroup analysis*, *Pooled (random)		
Mean difference serum calcium pre-/post-cinacalcet	Serum creatinine (µmol/L)	
< 0.27 mmol/L [12, 23, 25]	0.3 (-9.0 to 9.6), p=0.95	0.6,0%
≥0.27 mmol/L [14, 18, 22, 24]	-5.6 (-8.6 to -2.5), p<0.0001	0.5, 0%
Sensitivity analysis	Hedges's *g*	
All persistent HPT [10, 12, 14, 16-18, 22-25]	-0.100 (-0.193 to -0.007), p=0.035	0.055, 46%

Figure 1: QUOROM flow diagram

(1157 articles found, of these 1052 could be excluded by heading)

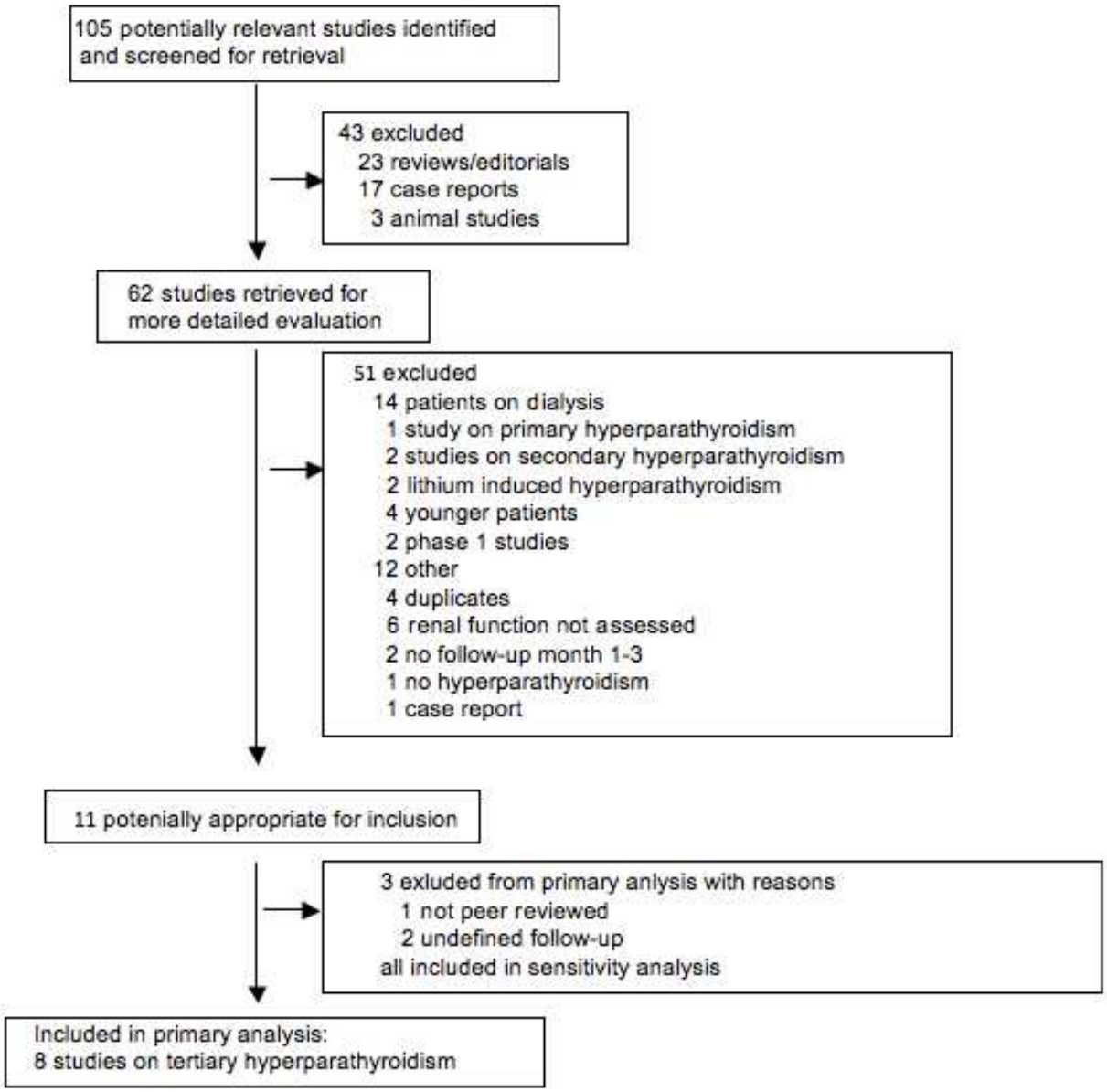
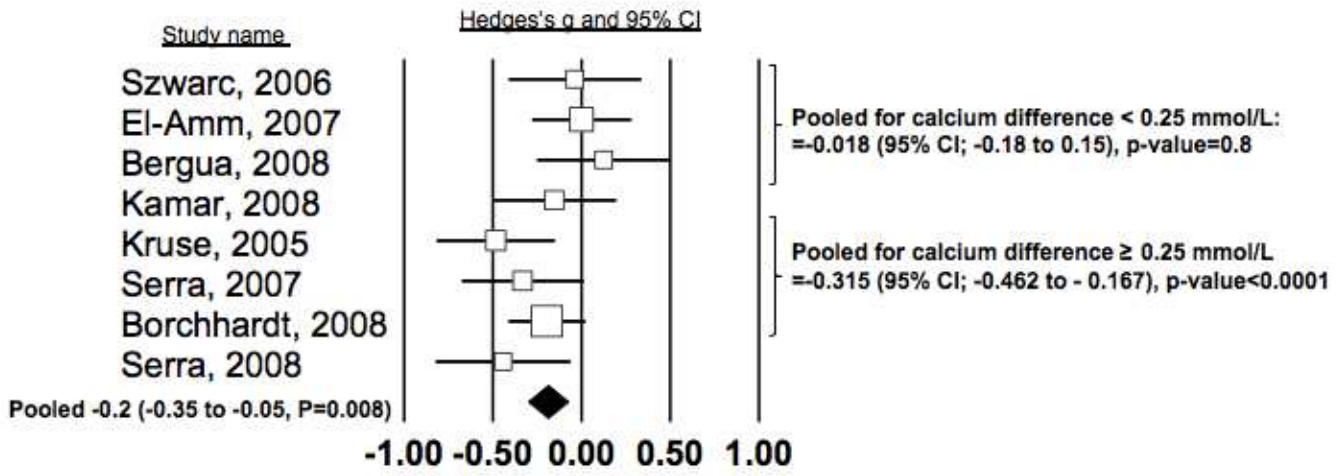
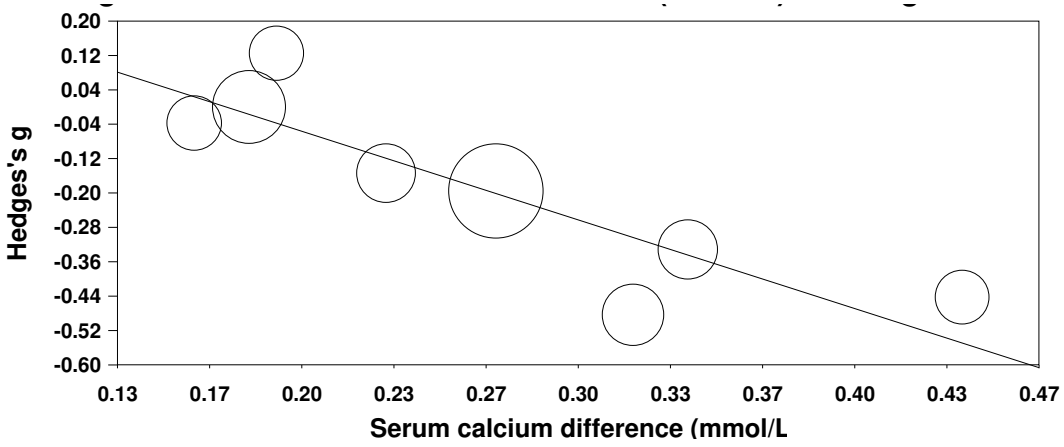


Figure 2. Change of renal function during cinacalcet treatment in renal allograft recipients with persistent hyperparathyroidism.



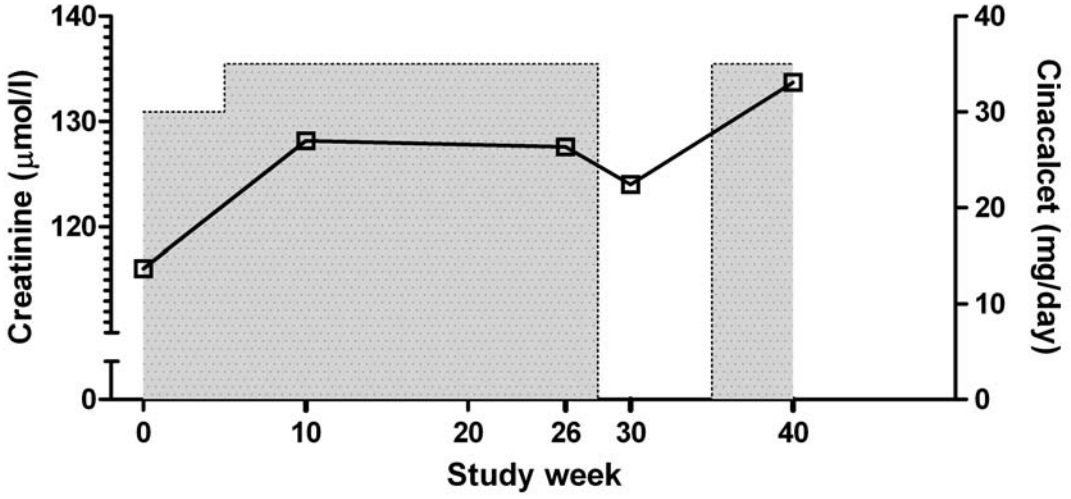
Legend Figure 2: Forest plot for Hedges's *g* for change in serum creatinine or creatinine clearance during cinacalcet treatment. Size of squares is proportional to the number of study participants. Error bars represent the 95% confidence intervals. The confidence limits for the pooled change in renal function are indicated by the diamond-shaped figure. There was no significant heterogeneity (Q-test p-value: 0.16). Among renal allograft recipients with post-transplant persistent HPT, the pooled Hedges's g was -0.188 (95% CI, -0.327 to -0048), p-value = 0.008).

Figure 3. Association between change in serum calcium levels and decline in renal function in patients with persistent hyperparathyroidism 3 months after initiation of cinacalcet treatment.



L**egend Figure 3:** Random effects meta-regression for change in serum creatinine or creatinine clearance (Hedges's *g)* on delta serum calcium during cinacalcet treatment (β=–2.05, p=0.004). Size of circles is proportional to the number of study participants.

Figure 4.
Mean serum creatinine values in 10 kidney allograft recipients with persistent hyperparathyroidism after cinacalcet treatment start, withdrawal and cinacalcet re-exposure.



L**egend Figure 4:** Mean serum creatinine values increased by 12 µmol/l (95% CI 40 to -16) and 11 µmol/l (95% CI 40 to -16) and estimated GFR (MDRD) decreased by 6 ml/min (95% CI -20 to 8) and 6 ml/min (95% CI -21 to 8) after cinacalcet initiation at week 0 and cinacalcet re-exposure at week 30, respectively.