Systematic review

Systematic review of surgical and medical treatment for tertiary hyperparathyroidism

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Background: **A significant proportion of patients with chronic kidney disease and secondary hyperparathyroidism (HPT) remain hyperparathyroid after kidney transplantation, a state known as tertiary HPT. Without treatment, tertiary HPT can lead to diminished kidney allograft and patient survival. Parathyroidectomy was commonly performed to treat tertiary HPT until the introduction of the calcimimetic drug, cinacalcet. It is not known whether surgery or medical treatment is superior for tertiary HPT.**

Methods: **A systematic review was performed and medical literature databases were searched for studies on the treatment of tertiary HPT that were published after the approval of cinacalcet.**

Results: **A total of 1669 articles were identified, of which 47 were included in the review. Following subtotal and total parathyroidectomy, initial cure rates were 98·7 and 100 per cent respectively, but in 7·6 and 4 per cent of patients tertiary HPT recurred. After treatment with cinacalcet, 80·8 per cent of the patients achieved normocalcaemia. Owing to side-effects, 6·4 per cent of patients discontinued cinacalcet treatment. The literature regarding graft function and survival is limited; however, renal graft survival after surgical treatment appears comparable to that obtained with cinacalcet therapy.**

Conclusion: **Side-effects and complications of both treatment modalities were mild and occurred in a minority of patients. Surgical treatment for tertiary HPT has higher cure rates than medical therapy.**

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Introduction

Hyperparathyroidism (HPT) is a disease caused by excessive secretion of parathyroid hormone (PTH) due to either parathyroid hyperplasia or adenomas. In primary HPT, enlargement of one or more of the parathyroid glands causes overproduction of PTH, resulting in hypercalcaemia, which can cause a variety of clinical symptoms. Surgery is currently the treatment of choice for patients fulfilling the criteria as defined by the guidelines of the fourth international workshop on asymptomatic primary HPT[1]. A targeted surgical approach, with a mini-incision, is considered the standard treatment[2–4].

In secondary HPT, hypocalcaemia and phosphate retention stimulate the parathyroid glands, resulting in parathyroid hyperplasia and increased PTH concentrations. Secondary HPT is one of the first metabolic complications of chronic kidney disease (CKD) and has been associated with untoward effects such as renal bone disease, increased cardiovascular morbidity and death from (cardio)vascular calcifications[5,6]. Successful kidney transplantation can reverse secondary HPT[7]. The greatest decline in serum PTH concentration is observed during the first 3 months after kidney transplantation, with a more gradual decline during the rest of the first post-transplant year[8,9]. Unfortunately, 1 year after an otherwise successful transplant, 17–50 per cent of transplanted patients still have HPT, which is unlikely to improve spontaneously[8,10]. This condition is referred to as tertiary or post-transplant HPT[7,11]. Treatment of tertiary HPT is important as raised serum calcium levels and hypercalciuria increase the risk of renal allograft dysfunction[12] and graft loss[13]. In addition, tertiary HPT is a major risk factor for bone fractures during the first 5 years after transplantation[14].

Historically, secondary and tertiary HPT were treated surgically. However, since 2004 medical treatment with

the calcimimetic agent cinacalcet (Mimpara®; Amgen, Thousand Oaks, California, USA) has gained popularity[15]. Cinacalcet increases the sensitivity of the calcium-sensing receptor of the parathyroid gland, thereby suppressing the production of PTH[16]. The drug was approved for the treatment of secondary HPT by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2004. However, it has not been approved to treat tertiary HPT. Nonetheless, off-label use of cinacalcet for tertiary HPT has increased, and in small non-randomized studies with short follow-up the drug appears to be safe, with gastrointestinal intolerance being the most common side-effect[17]. At present, there is only limited literature to guide clinicians faced with making treatment decisions regarding tertiary HPT. The aim of this systematic review was to compare the outcomes of surgical and medical treatment of tertiary HPT.

Methods

A systematic search for articles on the treatment of tertiary HPT was conducted. The definition of tertiary HPT varies in international literature, and includes serum PTH levels more than twice the upper limit of normal and persistent hypercalcaemia with increased PTH concentration after successful kidney transplantation[14,18]. In the present study, all definitions used were included.

The aim was to compare the outcomes of surgical and medical treatment of tertiary HPT. Primary endpoints were cure rate (defined as normalization of hypercalcaemia), recurrent tertiary HPT (definition of recurrence dependent on the definition of tertiary HPT used), and the complications and side-effects of each treatment modality. In addition, the impact of surgical and medical therapy on renal allograft function and survival was assessed. Publications were selected using MEDLINE, Embase, Web of Science, the Cochrane Library, PubMed Publisher and Google Scholar. Articles had to be original full-text articles written in English, published after 2004 (when cinacalcet received FDA/EMA regulatory approval) and describing an adult human population. To ascertain that no surgical trials were missed, the search strategy was extended to include articles published before 2004. No additional studies comparing surgical treatments for tertiary HPT were identified.

Articles describing treatment of tertiary HPT, both surgical and medical, were included, as well as articles describing renal function after initiation of these therapies. The following search terms were used: Hyperparathyroidism, Parathyroid hormone, Kidney/renal transplantation, Calcimimetic/Cinacalcet/Mimpara, Parathyroidectomy/Endocrine surgery.

Two authors were involved in selecting articles. Any disagreement was discussed until consensus was reached.

Methodological quality of included case–control and cohort studies was assessed by means of the Newcastle–Ottawa scale[19]. A score of 7–9 was considered high quality, and a score of 4–6 as fair quality. An 18-criteria checklist developed by Moga and colleagues[20] served to assess the quality of included case series. Here, a maximum of 18 points could be rewarded to each study. A score of 14–18 was considered high quality, and a score of 9–13 as fair quality. RCTs were assessed by means of the 25-item checklist of the CONSORT statement[21].

Statistical analysis

No meta-analysis could be performed owing to the lack of sufficient RCTs. When similar studies reported individual data regarding similar endpoints, data were pooled and percentages for the outcome of interest were calculated. Descriptive statistics reported in the tables consist of absolute numbers of patients and follow-up. No other statistical analysis was applied.

Results

The primary search identified 2963 records, with 16 records identified through reference search. After exclusion of duplicates, publication dates and case reports, reviews, letters to the editor and conference abstracts, all titles and abstracts were screened. Eventually, the full text of 232 articles was sought to assess eligibility. Following exclusions at this stage, a total of 47 articles were finally included in the review (*Fig. 1*).

Surgical management of tertiary hyperparathyroidism

Fourteen studies described the outcome after parathyroidectomy for tertiary HPT. These included one RCT[22], three prospective cohort studies[23–25], nine retrospective cohort studies[26–34] and one case series[35] (*Table 1*). Of the 13 observational studies, seven were considered of high quality and six fair quality. Group sizes differed between 15 and 136 patients, and follow-up ranged from a minimum of 9 months to as long as 116 months after transplantation.

Data regarding persistent or recurrent tertiary HPT after parathyroidectomy was available for 240 patients[25–28,30]. Seventy-one (29·6 per cent) of these patients had undergone a total parathyroidectomy either with (28 patients) or

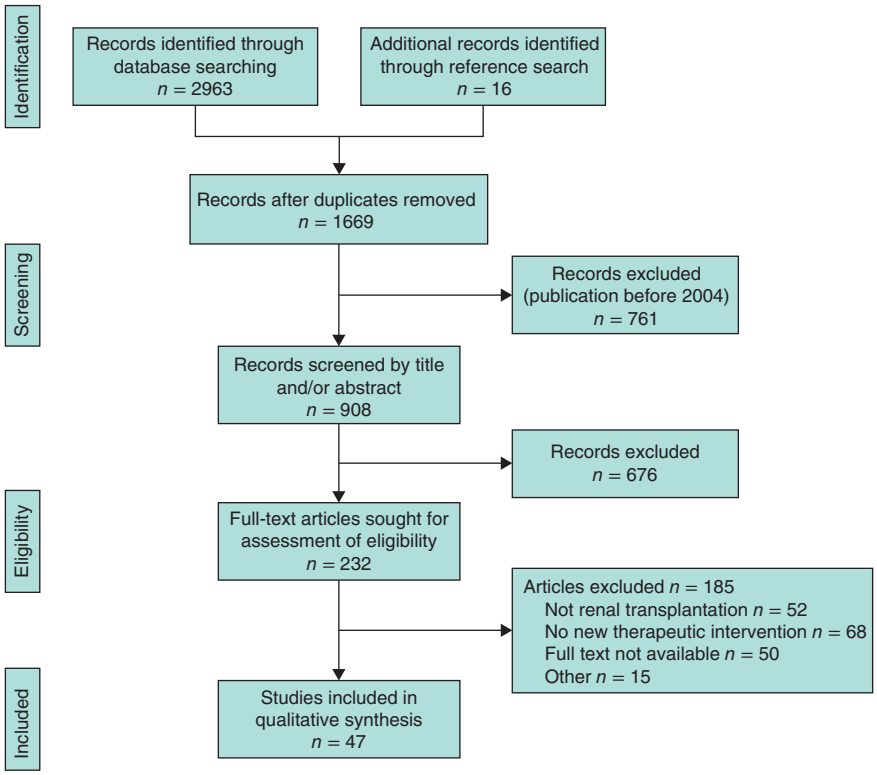

Fig. 1 Flow diagram of articles included in the systematic review

without (43) autotransplantation. No patient had persistent disease, although three (4 per cent) developed recurrent disease after a mean follow-up of 31–79 months. These three patients had all had a total parathyroidectomy without autotransplantation. A subtotal parathyroidectomy was performed in 158 of the 240 patients (65·8 per cent), of whom two (1·3 per cent) had persisting tertiary HPT and 12 (7·6 per cent) were found to have recurrent disease after a mean follow-up of 41–79 months. The remaining 11 patients (4·6 per cent) had undergone a limited parathyroidectomy, of whom ten (91 per cent) had persistent or recurrent disease (not specified). A surgical procedure was defined as limited parathyroidectomy when fewer than four glands were identified or when only one or two glands were removed deliberately.

Persisting disease was defined as persistent hypercalcaemia in two studies[28,30], with no definition in the other studies. Recurrent disease was defined as recurrent hypercalcaemia 6 months after surgery in two studies[28,30], with no definition in the other studies.

There were two patients (0·7 per cent of 274) who developed chronic hypocalcaemia. Transient hypocalcaemia[24,28,30–32,34] was observed in 15–23 per cent of the patients. One study[24], however, reported a rate of 67 per cent (8 of 12 patients) after total parathyroidectomy.

Complications after surgery, besides hypocalcaemia or persistent disease[28,30,32,33], were rare. Vocal cord paralysis, probably due to damage of the recurrent nerve, was seen in six of 280 patients (2·1 per cent). Other rare complications were pneumonia (3 of 280) and postoperative haematoma (2 of 280). No studies directly compared the different surgical strategies (subtotal parathyroidectomy, total parathyroidectomy with or without autotransplantation).

Medical management of tertiary hyperparathyroidism with cinacalcet

The experience with cinacalcet after kidney transplantation was reported in 24 articles: two RCTs[22,36] and 22 smaller observational studies[37–58] (*Table 2*). Of the 22 observational studies, nine were considered of high quality, and 13 were considered fair quality. The indication to prescribe cinacalcet was hypercalcaemic tertiary HPT in 22 studies, normocalcaemic tertiary HPT in one study, and both hypercalcaemic and normocalcaemic tertiary HPT in one study. A total of 713 patients were treated during a wide

Table 1 Summary of included studies reporting on treatment on tertiary hyperparathyroidism with parathyroidectomy

Reference	Study design	Procedure	No. of patients	Mean follow-up (months)	Persisting disease	Recurrent disease	Persistent hypocalcaemia	Study quality*
Kebebew *et al.*[34]	Retrospective cohort	SPTx	27	57·6	n.a.	n.a.	0	6 of 9
		Unilateral	7				0	
Triponez *et al.*[30]	Retrospective cohort	SPTx	70	67·2	0	1	1	6 of 9
Gilat *et al.*[32]	Retrospective cohort	SPTx	13	24	n.a.	n.a.	n.a.	7 of 9
		LTPTx	5					
		SR	2					
Triponez *et al.*[28]	Retrospective cohort	SPTx	72	64·8	n.a.	8§	0	9 of 9
		LTPTx	11			10§	0	
Evenepoel *et al.*[29]	Retrospective cohort	SPTx	74	n.a.	n.a.	n.a.	n.a.	9 of 9
		TPTx + AT	6					
		Unknown	10					
Rayes *et al.*[26]	Retrospective cohort	TPTx	17	31	0	0	0	9 of 9
		SPTx	16	41	2	3	0	
Schlosser *et al.*[35]	Case series	Primary	46	Range 9–116	n.a.	n.a.	n.a.	13 of 18†
		Redo	23					
Drakopoulos *et al.*[24]	Prospective cohort	TPTx	12	n.a.	n.a.	n.a.	n.a.	7 of 9
Pitt *et al.*[33]	Retrospective cohort	SPTx or TPTx	107	79	n.a.	n.a.	7%	9 of 9
		Limited	29				0	
Coulston *et al.*[31]	Retrospective cohort	TPTx	20	31	n.a.	n.a.	n.a.	6 of 9
Santos *et al.*[25]	Prospective cohort	TPTx + AT	28	42·9	0	0	1	6 of 9
Sadideen *et al.*[27]	Retrospective cohort	TPTx	26	60	0	3	0	6 of 9
Jager *et al.*[23]	Prospective cohort	TPTx + AT	15	24	n.a.	n.a.	n.a.	7 of 9
		LTPTx	8	24	n.a.	n.a.	n.a.	
Cruzado *et al.*[22]	RCT	SPTx	15	12	n.a.	n.a.	n.a.	20 of 25‡

*Newcastle–Ottawa scale[19] quality assessment unless indicated otherwise; †Moga quality assessment[20] and ‡CONSORT checklist[21]. §Indicates both persisting and recurrent disease (not specified). SPTx, subtotal parathyroidectomy; n.a., not available; LTPTx, less than total parathyroidectomy; SR, selective resection; TPTx, total parathyroidectomy; AT, autotransplantation.

Table 2 Summary of included studies reporting on treatment of tertiary hyperparathyroidism with cinacalcet

Reference	Study design	No. of patients	Mean follow-up (months)	Normocalcaemia	Discontinued treatment	Study quality*
Kruse *et al.*[38]	Case series	14	3	12	1	15 of 18
Serra *et al.*[42]	Case series	11	2·5	11	1	14 of 18
Apostolou *et al.*[37]	Case series	7	Range 3–18	n.a.	0	13 of 18
Leca *et al.*[39]	Retrospective cohort	10	12	n.a.	0	6 of 9†
Srinivas *et al.*[57]	Case series	11	Range 3–18	8	2	13 of 18
Szwarc *et al.*[46]	Case series	9	6	n.a.	3	13 of 18
Bergua *et al.*[47]	Case series	13	6	n.a.	n.a.	12 of 18
El-Amm *et al.*[43]	Case series	18	6	n.a.	1	14 of 18
Bergua *et al.*[56]	Case series	9	12	n.a.	1	15 of 18
Serra *et al.*[44]	Case series	10	0·5	n.a.	n.a.	12 of 18
Carrasco *et al.*[40]	Case series	14	6	n.a.	2	13 of 18
Gómez Marqués *et al.*[45]	Retrospective cohort	48	12	13	4	7 of 9†
López *et al.*[48]	Case series	29	Range 3–29	27	1	14 of 18
Toro Prieto *et al.*[49]	Case series	27	6	n.a.	n.a.	14 of 18
Borchhardt *et al.*[55]	Case series	10	Range 18–34	10	n.a.	13 of 18
Borstnar *et al.*[41]	Case series	11	12	n.a.	1	12 of 18
Copley *et al.*[50]	Case series	41	3–6	10 of 36	n.a.	12 of 18
Schwarz *et al.*[54]	Case series	58	12	53	4	15 of 18
Courbebaisse *et al.*[52]	Retrospective cohort	34	12	n.a.	n.a.	9 of 9†
Paschoalin *et al.*[58]	Case series	23	53	n.a.	0	12 of 18
Paschoalin *et al.*[51]	Case series	41	31	41	0	11 of 18
Evenepoel *et al.*[36]	RCT	57	12	45	5	19 of 25‡
Torregrosa *et al.*[53]	Retrospective cohort	193	22	n.a.	10	6 of 9†
Cruzado *et al.*[22]	RCT	15	12	10	1	20 of 25‡

*Moga quality assessment[20] unless indicated otherwise; †Newcastle–Ottawa scale[19] quality assessment and ‡CONSORT checklist[21]. n.a., Not available.

Table 3 Summary of included studies reporting on renal graft function after parathyroidectomy

Reference	Study design	Procedure	Mean follow-up (months)	No. of patients	Effect of parathyroidectomy on renal function	Study quality*
Evenepoel *et al.*[62]	Retrospective case–control	n.a.	6	32	Significant decline in renal function	7 of 9
Garcia *et al.*[66]	Retrospective	TPTx + AT	24	22	Deterioration until 3 months; return to baseline at 12 months	6 of 9
Evenepoel *et al.*[29]	Retrospective case–control	SPTx/TPTx	62	90	Deterioration at 1 month; return to baseline at 12 months	9 of 9
Schlosser *et al.*[61]	Retrospective	TPTx ± AT/SPTx/limited	12	69	Significant decrease in renal function in TPTx group	9 of 9
Schwarz *et al.*[64]	Retrospective cohort	SPTx/TPTx ± AT	n.a.	76	47% had deterioration of renal function; 10-year survival equal to that of patients with stable renal function	8 of 9
Rayes *et al.*[26]	Retrospective cohort	SPTx/TPTx	31/41	33	Short-term increase in creatinine; long-term return to baseline values	9 of 9
Kandil *et al.*[18]	Retrospective case–control	n.a.	36	19	Decrease in renal function at 3 years; no effect on graft survival	7 of 9
Ferreira *et al.*[60]	Retrospective case–control	TPTx ± AT	24	19	Short-term deterioration in renal function; long-term stabilization and return to baseline values	7 of 9
Jager *et al.*[63]	Retrospective cohort	Limited/SPTx/TPTx + AT	60	83	Decrease in renal function at all time points, less severe in LTPTx group	9 of 9
Jeon *et al.*[9]	Retrospective case–control	SPTx/TPTx	12	63	Acute deterioration of renal function, not returning to baseline at 12 months	9 of 9
Yang *et al.*[65]	Retrospective cohort	Limited/SPTx/TPTx + AT	n.a.	18	No change in renal function	8 of 9
Parikh *et al.*[59]	Retrospective cohort	SPTx	12	32	Transient kidney allograft dysfunction with recovery at 12 months	8 of 9

*Newcastle–Ottawa scale[19] quality assessment. n.a., Not available; TPTx, total parathyroidectomy; AT, autotransplantation; SPTx, subtotal parathyroidectomy.

range of periods (from 2 weeks up to 53 months) after renal transplantation. All studies showed a decline in mean serum calcium and PTH concentrations. Eleven studies, including 297 patients, described the outcome 'achieving normocalcaemia'. Of these patients, 240 (80·8 per cent) achieved normocalcaemia, with individual studies reporting rates ranging from 28 per cent (10 of 36) to 100 per cent[22,36,38,42,45,48,50,51,54,55,57]. Overall, of 578 patients treated with cinacalcet, 37 (6·4 per cent) discontinued treatment due to persisting hypercalcaemia or side-effects such as hypocalcaemia, gastrointestinal complaints or paraesthesia. Dose of cinacalcet ranged between 30 and 180 mg daily. No subgroups according to dosage were described.

Effect of surgery for tertiary hyperparathyroidism on renal graft function

Twelve studies[9,18,26,29,59–66] described the effect of parathyroidectomy for tertiary HPT on renal function after kidney transplantation (*Table 3*). Eleven of the 12 articles were considered of high quality, one article[66] was considered fair quality. In these studies, group sizes varied between 18 and 90 patients. Follow-up ranged from 6 to 62 months, with one exception[64] describing 10-year follow-up. One study reported stable renal function after parathyroidectomy; in five studies a transient decline in renal function was observed; and in six a permanent decline in renal function was reported. Interpretation of these studies is hampered by the lack of control groups. The two retrospective

Table 4 Summary of included studies reporting on renal graft function after treatment with cinacalcet

Reference	Study design	Mean follow-up (months)	No. of patients	Effect of cinacalcet on renal function	Study quality*
Carrasco *et al.*[40]	Case series	6	14	Stable creatinine	13 of 18†
Schwarz *et al.*[54]	Case series	12	58	Rise in serum creatinine of 13 μmol/l	15 of 18†
Courbebaisse *et al.*[52]	Retrospective cohort	12	34	Stable creatinine	9 of 9
Yang *et al.*[65]	Retrospective cohort	12	13	Mean creatinine increase of 0·056 mg/dl in 1 year	8 of 9
Torregrosa *et al.*[53]	Retrospective cohort	22	193	Stable creatinine	6 of 9

*Newcastle–Ottawa scale[19] quality assessment unless indicated otherwise; †Moga quality assessment[20].

studies that compared patients undergoing parathyroidectomy with a matched cohort showed either a permanent decline at 6 months' follow-up[62] or a transient decline in renal function with 24 months' follow-up[60].

Two studies[18,64] addressed the effect of parathyroidectomy on graft survival. Although a permanent decline in renal function was observed in many patients having parathyroidectomy, this did not reduce graft survival when compared with that following parathyroidectomy in patients with no decline in renal function, with a follow-up of 3 and 10 years respectively[18,64]. Furthermore 3- and 10-year graft survival rates were similar to those in patients undergoing renal transplantation without parathyroidectomy.

Effect of cinacalcet for tertiary hyperparathyroidism on renal graft function

Five articles[40,52–54,65] described the effect of cinacalcet on graft function after renal transplantation (*Table 4*). Three of these were considered of high quality, and two of fair quality. Three small studies[40,52,65] with a total of 61 patients, described stable graft function during treatment. This was confirmed by a large observational study by Torregrosa and co-workers[53] who found stable graft function during treatment with cinacalcet in a group of 193 patients with tertiary HPT.

In contrast, Schwarz *et al.*[54] described a cohort of 58 patients and observed a significant decline in estimated glomerular filtration rate of 9 per cent during treatment with cinacalcet. These studies did not report data on the effect of cinacalcet on graft survival or overall survival. No studies are available that directly compared medical therapy with surgical therapy.

Discussion

From this systematic review of studies reporting surgical and medical therapy with cinacalcet for tertiary HPT it can be concluded that surgical treatment has higher cure rates with low complication rates. The only RCT[22] comparing surgical therapy with medical therapy with cinacalcet included two cohorts of 15 patients, with the primary endpoint being normocalcaemia at 12 months. After parathyroidectomy 100 per cent of patients achieved normocalcaemia, compared with 10 of the 15 patients (67 per cent) treated with cinacalcet. This is the only RCT to date, and therefore it was not possible to perform a meta-analysis. Unfortunately, trials focusing on major clinical endpoints are lacking, and in the available literature regarding this topic there is no uniform definition regarding tertiary HPT.

With regard to surgical treatment, three procedures are commonly performed: total parathyroidectomy with or without autotransplantation, subtotal parathyroidectomy, and limited parathyroidectomy. An international survey among 86 endocrine surgeons[67] reported that 85 (99 per cent) performed a (sub)total parathyroidectomy with or without autotransplantation for secondary or tertiary HPT. A limited approach, when only enlarged parathyroid glands are removed, was rarely used. Although there are no studies directly comparing these procedures, persisting and recurrent disease rates shown in the present review indicate that limited parathyroidectomy should be avoided: 4, 8·9 and 91 per cent for total, subtotal and limited resection respectively.

Renal function after parathyroidectomy for tertiary HPT seems to decline transiently or permanently. In cohorts of patients undergoing renal transplant, overall allograft function will decline eventually. Whether this decline in function is due to the parathyroidectomy or to chronic rejection can be determined only from studies with a control group. At present, no such studies are available. The studies in the present review show that there is no effect of parathyroidectomy on overall graft survival[18,64]. Surgical complications are rare, and parathyroidectomy appears to be a safe and feasible treatment option for tertiary HPT. Unfortunately, the literature regarding this topic is sparse, consisting mostly of case series or cohort studies.

Medical treatment of tertiary HPT with cinacalcet significantly decreases serum calcium concentrations, but only 80·8 per cent of the patients achieved normocalcaemia and

6·4 per cent discontinued treatment due to side-effects such as gastrointestinal intolerance. Renal graft function is stable during treatment with cinacalcet or may decline minimally. A meta-analysis of observational studies by Henschkowski and colleagues[68] reported an increase in serum creatinine levels of 5 μmol/l after 3 months of treatment with cinacalcet; no long-term data are available from this study. Again, the literature consisted mostly of observational studies, with only nine of 22 studies being considered of high quality.

The present endpoints did not focus on cardiovascular morbidity or mortality, although this is an important complication for all patients undergoing dialysis or renal transplantation. Included studies did not report data regarding the effect of parathyroidectomy or cinacalcet on cardiovascular complication rates in patients with tertiary HPT. However, there is some evidence from patients with secondary HPT. In this group, parathyroidectomy leads to a decreased risk of major cardiovascular events and death in comparison with conservative treatment[69,70]. Furthermore, in 2012 the results of the EVOLVE trial[71], which randomized patients with secondary HPT to best medical treatment or best medical treatment plus cinacalcet, were published. The addition of cinacalcet did not reduce the risk of death or major cardiovascular events. In addition, a meta-analysis of RCTs[72] reported that the use of cinacalcet in patients undergoing dialysis did not improve overall survival. Cardiovascular morbidity and mortality in patients with tertiary HPT should be a focus of future trials.

Another important complication for patients with tertiary HPT is bone disease. The rate of osteoporosis is high in patients with a renal transplant[73–79], and tertiary HPT is associated with an increased risk of osteoporosis[73], and a major risk for fractures[14]. Small trials[41,49,80–83] have suggested that parathyroidectomy increases bone mineral density, in contrast to cinacalcet. The development of osteoporosis should also be a focus of future trials.

Finally, cost-effectiveness remains an important consideration in the choice of treatment. Uncontrolled HPT increases the economic burden of patients with secondary HPT undergoing dialysis owing to higher medication and hospitalization costs[84]. Compared with cinacalcet treatment, parathyroidectomy is more cost-effective in these patients[85], mainly due to the significant additional cost and chronic use of cinacalcet. Currently, there are no data regarding cost-effectiveness in treatments for tertiary HPT.

Although high-quality evidence is lacking, this systematic review shows that surgical treatment for HPT appears to be more effective than medical treatment. Furthermore, complication rates after surgery are low and graft survival is comparable to that obtained with cinacalcet. Higher-quality data on important clinical endpoints such as cardiovascular morbidity and renal bone disease are lacking. Future research should include randomized trials focusing on clinical endpoints such as quality of life, cardiovascular morbidity and renal bone disease, so that the optimal treatment for an individual patient can be chosen.

Disclosure

The authors declare no conflict of interest.

References

1 Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C *et al*. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99**: 3561–3569.

2 Slepavicius A, Beisa V, Janusonis V, Strupas K. Focused *versus* conventional parathyroidectomy for primary hyperparathyroidism: a prospective, randomized, blinded trial. *Langenbecks Arch Surg* 2008; **393**: 659–666.

3 Russell CF, Dolan SJ, Laird JD. Randomized clinical trial comparing scan-directed unilateral *versus* bilateral cervical exploration for primary hyperparathyroidism due to solitary adenoma. *Br J Surg* 2006; **93**: 418–421.

4 Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. *Arch Surg* 2005; **140**: 472–478.

5 Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001; **12**: 2131–2138.

6 Schlieper G, Floege J. Calcimimetics in CKD – results from recent clinical studies. *Pediatr Nephrol* 2008; **23**: 1721–1728.

7 Evenepoel P. Recovery *versus* persistence of disordered mineral metabolism in kidney transplant recipients. *Semin Nephrol* 2013; **33**: 191–203.

8 Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B, Vanrenterghem Y. Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. *Nephrol Dial Transplant* 2004; **19**: 1281–1287.

9 Jeon HJ, Kim YJ, Kwon HY, Koo TY, Baek SH, Kim HJ *et al*. Impact of parathyroidectomy on allograft outcomes in kidney transplantation. *Transplant Int* 2012; **12**: 1248–1256.

10 Copley JB, Wüthrich RP. Therapeutic management of post-kidney transplant hyperparathyroidism. *Clin Transplant* 2011; **25**: 24–39.

11 Gioviale MC, Bellavia M, Damiano G, Lo Monte AI. Post-transplantation tertiary hyperparathyroidism. *Ann Transplant* 2012; **17**: 111–119.

12 Ozdemir FN, Afsar B, Akgul A, Usluogullari C, Akcay A, Haberal M. Persistent hypercalcemia is a significant risk factor for graft dysfunction in renal transplantation recipients. *Transplant Proc* 2006; **38**: 480–482.
13 Egbuna OI, Taylor JG, Bushinsky DA, Zand MS. Elevated calcium phosphate product after renal transplantation is a risk factor for graft failure. *Clin Transplant* 2007; **21**: 558–566.
14 Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duvel C *et al*. Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. *Am J Transplant* 2012; **13**: 2653–2663.
15 Wüthrich RP, Martin D, Bilezikian JP. The role of calcimimetics in the treatment of hyperparathyroidism. *Eur J Clin Invest* 2007; **37**: 915–922.
16 Brown EM. Clinical utility of calcimimetics targeting the extracellular calcium-sensing receptor (CaSR). *Biochem Pharmacol* 2010; **80**: 297–307.
17 Cohen JB, Gordon CE, Balk EM, Francis JM. Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: a systematic review and meta-analysis. *Transplantation* 2012; **94**: 1041–1048.
18 Kandil E, Florman S, Alabbas H, Abdullah O, McGee J, Noureldine S *et al*. Exploring the effect of parathyroidectomy for tertiary hyperparathyroidism after kidney transplantation. *Am J Med Sci* 2010; **339**: 420–424.
19 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al*. *The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses*. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [accessed 20 March 2017].
20 Moga C, Guo B, Schopflocher D, Harstall C. *Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphie Technique*. Institute of Health Economics: Edmonton, 2012.
21 Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; **152**: 726–732.
22 Cruzado JM, Moreno P, Torregrosa JV, Taco O, Mast R, Gómez-Vaguero C *et al*. A randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. *J Am Soc Nephrol* 2016; **27**: 2487–2494.
23 Jager MD, Emmanouilidis N, Jackobs S, Kespohl H, Hett J, Musatkin D *et al*. Presence of small parathyroid glands in renal transplant patients supports less-than-total parathyroidectomy to treat hypercalcemic hyperparathyroidism. *Surgery* 2014; **155**: 22–32.
24 Drakopoulos S, Koukoulaki M, Apostolou T, Pistolas D, Balaska K, Gavriil S *et al*. Total parathyroidectomy without autotransplantation in dialysis patients and renal transplant recipients, long-term follow-up evaluation. *Am J Surg* 2009; **198**: 178–183.
25 Santos RO, Ohe MN, Carvalho AB, Neves MC, Kunii I, Lazaretti-Castro M *et al*. Total parathyroidectomy with presternal intramuscular autotransplantation in renal patients: a prospective study of 66 patients. *J Osteoporos* 2012; **2012**: 631243.
26 Rayes N, Seehofer D, Schindler R, Reinke P, Kahl A, Ulrich F *et al*. Long-term results of subtotal *vs* total parathyroidectomy without autotransplantation in kidney transplant recipients. *Arch Surg* 2008; **143**: 756–761.
27 Sadideen HM, Taylor JD, Goldsmith DJ. Total parathyroidectomy without autotransplantation after renal transplantation for tertiary hyperparathyroidism: long-term follow-up. *Int Urol Nephrol* 2012; **44**: 275–281.
28 Triponez F, Kebebew E, Dosseh D, Duh QY, Hazzan M, Noel C *et al*. Less-than-subtotal parathyroidectomy increases the risk of persistent/recurrent hyperparathyroidism after parathyroidectomy in tertiary hyperparathyroidism after renal transplantation. *Surgery* 2006; **140**: 990–999.
29 Evenepoel P, Claes K, Kuypers DR, Debruyne F, Vanrenterghem Y. Parathyroidectomy after successful kidney transplantation: a single centre study. *Nephrol Dial Transplant* 2007; **22**: 1730–1737.
30 Triponez F, Dosseh D, Hazzan M, Noel C, Vanhille P, Proye CA. Subtotal parathyroidectomy with thymectomy for autonomous hyperparathyroidism after renal transplantation. *Br J Surg* 2005; **92**: 1282–1287.
31 Coulston JE, Egan R, Willis E, Morgan JD. Total parathyroidectomy without autotransplantation for renal hyperparathyroidism. *Br J Surg* 2010; **97**: 1674–1679.
32 Gilat H, Feinmesser R, Vinkler Y, Morgenstern S, Shvero J, Bachar G *et al*. Clinical and operative management of persistent hyperparathyroidism after renal transplantation: a single-center experience. *Head Neck* 2007; **29**: 996–1001.
33 Pitt SC, Panneerselvan R, Chen H, Sippel RS. Tertiary hyperparathyroidism: is less than a subtotal resection ever appropriate? A study of long-term outcomes. *Surgery* 2009; **146**: 1130–1137.
34 Kebebew E, Duh QY, Clark OH. Tertiary hyperparathyroidism – histologic patterns of disease and results of parathyroidectomy. *Arch Surg* 2004; **139**: 974–977.
35 Schlosser K, Rothmund M, Maschuw K, Barth PJ, Vahl TP, Suchan KL *et al*. Graft-dependent renal hyperparathyroidism despite successful kidney transplantation. *World J Surg* 2008; **32**: 557–565.
36 Evenepoel P, Cooper K, Holdaas H, Messa P, Mourad G, Olgaard K *et al*. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am J Transplant* 2014; **14**: 2545–2555.
37 Apostolou T, Kollia K, Damianou L, Kaitsoiti H, Kotsiev V, Dracopoulos S *et al*. Hypercalcemia due to resistant hyperparathyroidism in renal transplant patients treated with the calcimimetic agent cinacalcet. *Transplant Proc* 2006; **38**: 3514–3516.

38 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.
39 Leca N, Laftavi M, Gundroo A, Kohli R, Min I, Karam J *et al*. Early and severe hyperparathyroidism associated with hypercalcemia after renal transplant treated with cinacalcet. *Am J Transplant* 2006; **6**: 2391–2395.
40 Carrasco FR, Pérez-Flores I, Calvo N, Ridao N, Sánchez A, Barrientos. Treatment of persistent hyperparathyroidism in renal transplant patients with cinacalcet improves control of blood pressure. *Transplant Proc* 2009; **41**: 2385–2387.
41 Borstnar S, Erzen B, Gmeiner Stopar T, Kocjan T, Arnol M, Kandus A *et al*. Treatment of hyperparathyroidism with cinacalcet in kidney transplant recipients. *Transplant Proc* 2010; **42**: 4078–4082.
42 Serra AL, Schwarz AA, Wick FH, Marti HP, Wüthrich RP. Successful treatment of hypercalcemia with cinacalcet in renal transplant recipients with persistent hyperparathyroidism. *Nephrol Dial Transplant* 2005; **20**: 1315–1319.
43 El-Amm JM, Doshi MD, Singh A, Migdal S, Morawski K, Sternbauer D *et al*. Preliminary experience with cinacalcet use in persistent secondary hyperparathyroidism after kidney transplantation. *Transplantation* 2007; **83**: 546–549.
44 Serra AL, Wuhrmann C, Wüthrich RP. Phosphatemic effect of cinacalcet in kidney transplant recipients with persistent hyperparathyroidism. *Am J Kidney Dis* 2008; **52**: 1151–1157.
45 Gómez Marqués G, Obrador Mulet A, Vilar Gimeno A, Pascual Felip MJ, Alarcón Zurita A, Molina Guasch M *et al*. Treatment with cinacalcet of secondary hyperparathyroidism after renal transplantation. *Transplant Proc* 2009; **41**: 2139–2143.
46 Szwarc I, Argiles A, Garrigue V, Delmas S, Chong G, Deleuze S *et al*. Cinacalcet chloride is efficient and safe in renal transplant recipients with posttransplant hyperparathyroidism. *Transplantation* 2006; **82**: 675–680.
47 Bergua C, Torregrosa JV, Cofan F, Oppenheimer F. Cinacalcet for the treatment of hypercalcemia in renal transplanted patients with secondary hyperparathyroidism. *Transplant Proc* 2007; **39**: 2254–2255.
48 López V, Toledo R, Sola E, Gutiérrez C, Sujan S, Rodríguez MA *et al*. Treatment with cinacalcet in 29 kidney transplant patients with persistent hyperparathyroidism. *Transplant Proc* 2009; **41**: 2394–2395.
49 Toro Prieto FJ, Bernal Blanco G, Navarro García M, Cabello Chaves V, Garciajiménez R, Pereira Palomo P *et al*. Calcimimetics and bone mineral density in renal transplant patients with persistent secondary hyperparathyroidism. *Transplant Proc* 2009; **41**: 2144–2147.
50 Copley JB, Germain M, Stern L, Pankewycz P, Katznelson S, Shah T *et al*. Evaluation of cinacalcet HCl treatment after kidney transplantation. *Transplant Proc* 2010; **42**: 2503–2508.
51 Paschoalin RP, Torregrosa JV, Barros X, Duran CE, Campistol JM. Cinacalcet *de novo* in persistent hypercalcemia after kidney transplantation secondary to hyperparathyroidism: long-term follow-up and effect of withdrawal. *Transplant Proc* 2012; **44**: 2376–2378.
52 Courbebaisse M, Diet C, Timsit MO, Mamzer MF, Thervet E, Noel LH *et al*. Effects of cinacalcet in renal transplant patients with hyperparathyroidism. *Am J Nephrol* 2012; **35**: 341–348.
53 Torregrosa JV, Morales E, Díaz JM, Crespo J, Bravo J, Gómez G *et al*. Cinacalcet for hypercalcaemic secondary hyperparathyroidism after renal transplantation: a multicentre, retrospective, 3-year study. *Nephrology* 2014; **19**: 84–93.
54 Schwarz A, Merkel S, Leitolf H, Haller H. The effect of cinacalcet on bone remodeling and renal function in transplant patients with persistent hyperparathyroidism. *Transplantation* 2011; **91**: 560–565.
55 Borchhardt KA, Diarra D, Sulzbacher I, Benesch T, Haas M, Sunder-Plassmann G. Cinacalcet decreases bone formation rate in hypercalcemic hyperparathyroidism after kidney transplantation. *Am J Nephrol* 2010; **31**: 482–489.
56 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.
57 Srinivas TR, Schold JD, Womer KL, Kaplan B, Howard RJ, Bucci CM *et al*. Improvement in hypercalcemia with cinacalcet after kidney transplantation. *Clin J Am Soc Nephrol* 2006; **1**: 323–326.
58 Paschoalin RP, Torregrosa JV, Sanchez-Escuredo A, Barros X, Duran CE, Campistol JM. Cinacalcet treatment for stable kidney transplantation patients with hypercalcemia due to persistent secondary hyperparathyroidism: a long-term follow-up. *Transplant Proc* 2012; **44**: 2588–2589.
59 Parikh S, Nagaraja H, Agarwal A, Samavedi S, Von Visger J, Nori U *et al*. Impact of post-kidney transplant parathyroidectomy on allograft function. *Clin Transplant* 2013; **27**: 397–402.
60 Ferreira GF, de Menezes Montenegro FL, Machado DJ, Ianhez LE, Nahas WC, David-Neto E. Parathyroidectomy after kidney transplantation: short- and long-term impact on renal function. *Clinics (Sao Paulo)* 2011; **66**: 431–435.
61 Schlosser K, Endres N, Celik I, Fendrich V, Rothmund M, Fernandez ED. Surgical treatment of tertiary hyperparathyroidism: the choice of procedure matters! *World J Surg* 2007; **31**: 1947–1953.
62 Evenepoel P, Claes K, Kuypers D, Maes B, Vanrenterghem Y. Impact of parathyroidectomy on renal graft function, blood pressure and serum lipids in kidney transplant recipients: a single centre study. *Nephrol Dial Transplant* 2005; **20**: 1714–1720.
63 Jager MD, Kaaden S, Emmanouilidis N, Luck R, Beckmann JH, Guner Z *et al*. Effect of incomplete parathyroidectomy preserving entire parathyroid glands on renal graft function. *Arch Surg* 2011; **146**: 704–710.
64 Schwarz A, Rustien G, Merkel S, Radermacher J, Haller H. Decreased renal transplant function after

parathyroidectomy. *Nephrol Dial Transplant* 2007; **22**: 584–591.
65 Yang RL, Freeman K, Reinke CE, Fraker DL, Kakakousis GC, Kelz RR *et al*. Tertiary hyperparathyroidism in kidney transplant recipients: characteristics of patients selected for different treatment strategies. *Transplantation* 2012; **94**: 70–76.
66 Garcia A, Mazuecos A, Garcia T, Gonzalez P, Ceballos M, Rivero M. Effect of parathyroidectomy on renal graft function. *Transplant Proc* 2005; **37**: 1459–1461.
67 Riss P, Asari R, Scheuba C, Niederle B. Current trends in surgery for renal hyperparathyroidism (RHPT) – an international survey. *Langenbecks Arch Surg* 2013; **398**: 121–130.
68 Henschkowski J, Bischoff-Ferrari HA, Wüthrich RP, Serra AL. Renal function in patients treated with cinacalcet for persistent hyperparathyroidism after kidney transplantation. *Kidney Blood Press Res* 2011; **34**: 97–103.
69 Costa-Hong V, Jorgetti V, Gowdak LH, Moyses RM, Krieger EM, De Lima JJ. Parathyroidectomy reduces cardiovascular events and mortality in renal hyperparathyroidism. *Surgery* 2007; **142**: 699–703.
70 Trombetti A, Stoermann C, Robert JH, Herrmann FR, Pennisi P, Martin PY *et al*. Survival after parathyroidectomy in patients with end-stage renal disease and severe hyperparathyroidism. *World J Surg* 2007; **31**: 1014–1021.
71 EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J *et al*. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; **367**: 2482–2494.
72 Palmer SC, Nistor I, Craig JC, Pellegrini F, Messa P, Tonelli M *et al*. Cinacalcet in patients with chronic kidney disease: a cumulative meta-analysis of randomized controlled trials. *PLoS Med* 2013; **10**: e1001436.
73 Akaberi S, Lindergard B, Simonsen O, Nyberg G. Impact of parathyroid hormone on bone density in long-term renal transplant patients with good graft function. *Transplantation* 2006; **82**: 749–752.
74 Tutal E, Uyar ME, Colak T, Bal Z, Demirci BG, Bozkurt T *et al*. Low graft function and ongoing hyperparathyroidism are closely related to post-transplantation osteoporosis. *Transplant Proc* 2013; **45**: 1562–1566.
75 Lim DST, Kee TYS, Fook-Chong S, Zhang RF, Chandran M. Prevalence and patterns of bone loss in the first year after renal transplant in South East Asian patients. *Transplantation* 2011; **92**: 557–563.
76 Gupta AK, Huang M, Ramesh Prasad GV. Determinants of bone mineral density in stable kidney transplant recipients. *J Nephrol* 2012; **25**: 373–383.
77 Falkiewicz K, Boratynska M, Zmonarski SC, Milewicz A, Patrzalek D, Biecek P *et al*. Evolution of bone disease at 2 years after transplantation: a single-center study. *Transplant Proc* 2009; **41**: 3063–3066.
78 Bubenicek P, Sotornik I, Vitko S, Teplan V. Early bone mineral density loss after renal transplantation and pre-transplant PTH: a prospective study. *Kidney Blood Press Res* 2008; **31**: 196–202.
79 Lan G, Peng L, Xie X, Peng F, Wang Y, Yu S. Alendronate is effective to treat bone loss in renal transplantation recipients. *Transplant Proc* 2008; **40**: 3496–3498.
80 Chou FF, Hsieh KC, Chen YT, Lee CT. Parathyroidectomy followed by kidney transplantation can improve bone mineral density in patients with secondary hyperparathyroidism. *Transplantation* 2008; **86**: 554–557.
81 Sadideen H, Covic A, Goldsmith D. Mineral and bone disorder after renal transplantation: a review. *Int Urol Nephrol* 2008; **40**: 171–184.
82 Cho ME, Duan Z, Chamberlain CE, Reynolds JC, Ring MS, Mannon RB. Cinacalcet improves bone density in post-kidney transplant hyperparathyroidism. *Transplant Proc* 2010; **42**: 3554–3558.
83 Collaud S, Staub-Zahner T, Trombetti A, Clerici C, Marangon N, Binet I *et al*. Increase in bone mineral density after successful parathyroidectomy for tertiary hyperparathyroidism after renal transplantation. *World J Surg* 2008; **32**: 1795–1801.
84 Chiroli S, Mattin C, Belozeroff V, Perrault L, Mitchell D, Gioni I. Impact of mineral and bone disorder on healthcare resource use and associated costs in the European Fresenius medical care dialysis population: a retrospective cohort study. *BMC Nephrol* 2012; **13**: 140.
85 Narayan R, Perkins RM, Berbano EP, Yuan CM, Neff RT, Sawyers ES *et al*. Parathyroidectomy *versus* cinacalcet hydrochloride-based medical therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. *Am J Kidney Dis* 2007; **49**: 801–813.