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NEPHROLOGY – ORIGINAL PAPER

Total parathyroidectomy without autotransplantation after renal transplantation for tertiary hyperparathyroidism: long-term follow-up

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Abstract
Introduction Renal transplant patients are unique in that bone changes occur on a background of pre-existing chronic kidney disease-mineral bone disorder. In a few cases, there is overt hyperparathyroidism manifested by hypercalcaemia. Traditionally, if severe or persistent, this is treated by parathyroidectomy. At our unit, the default surgical operation is total parathyroidectomy without autotransplantation.
Methods Patient charts for the last three decades were reviewed retrospectively. Twenty-six subjects with functioning renal transplants who underwent parathyroidectomy had biochemistry and clinical information for at least 6 months pre- and post-surgery. The criteria for parathyroidectomy were persistent hypercalcaemia (>2.75 mmol/L) and/or clinical problems (e.g. kidney stones). A 5-year follow-up was available for all 26 subjects and a 9-year follow-up for 20 patients.
Results After surgery, patients were supplemented with 1-α-calcidol. The median preoperative calcium level was 3.10 mmol/L. One month postoperatively, this fell to 2.41 mmol/L. Normocalcaemia was maintained at 5 years (2.40 mmol/L) and at 9 years (2.39 mmol/L), with a calcium–phosphate product of 3.0 $mmol^2/L^2$ and median parathyroid hormone level of 12 pg/mL.
Conclusion Total parathyroidectomy without autotransplantation in renal transplant patients appears to be protective against persistent and recurrent disease. This is the largest series with the longest follow-up available in the literature of this specific patient population.

Keywords Tertiary hyperparathyroidism · Parathyroidectomy · Renal transplantation

Abbreviations

RTX	Renal transplantation
RTx	Renal transplant
PTH	Parathyroid hormone
PTX	Parathyroidectomy
HPT	Hyperparathyroidism
CKD-MBD	Chronic kidney disease-mineral bone disorder

Introduction

Renal transplantation (RTX) is the treatment of choice for most patients with end-stage renal disease (ESRD). Post-RTX bone disease is a well-known entity [1]. Immunosuppressive agents and persistence of hyperparathyroidism (HPT) have primarily been implicated in its aetiology. Renal transplant patients are unique in that the bone changes occur on a background of

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pre-existing chronic kidney disease-mineral bone disorder (CKD-MBD). The course of renal bone disease post-RTX depends on persisting abnormalities such as hypercalcaemia, hypophosphataemia, and impaired renal function, as well as on the type, dose and duration of immunosuppressive medications that are needed to minimise allograft rejection. These factors operate additively and their effects are often difficult to dissociate from the already existing CKD-MBD.

In a few cases, there is overt HPT post-RTX, which usually manifests as hypercalcaemia. This can cause clinical problems including fractures, renal stones and renal allograft dysfunction [2]. Traditionally, if severe or persistent, this is treated by parathyroidectomy (PTX). This may be in the form of total PTX with autotransplantation [3, 4], subtotal PTX [4, 5] or total PTX alone [6, 7].

There has been recent debate on the optimal form of PTX in these patients. The literature mainly reports the results of subtotal PTX or total PTX with autotransplantation, but more recently, the role of total PTX alone has been re-established.

In this study, we retrospectively reviewed the last three decades of renal transplant patients from our institution and characterised the effects of total PTX without autotransplantation on blood levels of minerals in patients with post-RTX HPT. We found 26 subjects who had undergone total PTX, for whom we had biochemistry and clinical data for at least 6 months pre- and post-operatively, with a minimum follow-up of 5 years.

Methods

Patients

A retrospective analysis was performed to identify RTx recipients who underwent PTX for tertiary HPT. Twenty-six total parathyroidectomies without autotransplantation were performed between September 1989 and May 2003. PTH levels in these patients were at least thrice the normal range. The criteria for proceeding to PTX were persistent hypercalcaemia >2.75 mmol/L (11 mg/dL) without any other identifiable reason, or its clinical manifestations (e.g. recurrent renal stones, severe athralgia and myalgia), despite adequate medical treatment.

Surgical technique

All procedures were performed or supervised by one of two consultant surgeons. The exposure was as per the well-documented approach to the thyroid and parathyroid glands via a transverse collar incision. Caution was exercised for preservation of the recurrent laryngeal nerve. All parathyroid glands that were visualised were removed and sent for histological confirmation. Thymectomies were not routinely performed.

Follow-up

All patients were followed up with blood tests post-operatively. All patients were on 0.25 mcg 1-α-calcidol post-operatively, for prophylaxis against hypocalcaemia, or higher doses when required, and 46% were also on calcium supplementation during follow-up. For the purposes of this study, the monitored parameters were serum, calcium, phosphate, PTH, and creatinine. As these can be seen as discontinuous variables, median levels were analysed. Serum levels were available for all patients immediately post-operatively (except for PTH), and at 1 month, 6 months, 1 year, 5 years (for all 26 patients) and 9 years (for 20 patients). The primary outcome used to measure the success of PTX was normocalcaemia (or, in effect, the absence of recurrent hypercalcaemia). Both imaging (ultrasonography and technetium-99m-sestamibi scanning) and intra-operative PTH level monitoring were not routinely available at the time this study began, and hence, no such data are included.

Results

The mean age of participants was 54 years. There were 15 women and 11 men, totalling 26 patients. The mean time post-RTX till PTX was 49 months. There was follow-up data available for all 26 subjects at 5 years, but only for 20 subjects at 9 years. Four subjects had passed away (due to cardiac and immunosuppressant-related complications) and 2 had an incomplete data set, and these patients were thus excluded. There were 2 cases of graft failure, not attributed to the PTX.

In the immediate post-operative period, all previously symptomatic patients had complete resolution of their symptoms of hypercalcaemia (i.e. arthralgia,

myalgia, bone ache and muscle weakness) and no major complications documented. There were no cases of fulminate clinical symptoms of hypocalcemia in this cohort and no hypocalcaemia-related deaths.

The mean number of parathyroid glands removed per patient was 3.8 (range 2–4). Histology confirmed all glands removed as parathyroids.

Table 1 summarises the median serum levels of biochemical parameters, pre- and post-operatively. For PTH specifically, the range is also shown. The Wilcoxon Mann–Whitney test was used to confirm statistical significance. A P value less than 0.05 was taken to be significant.

In summary, the median pre-operative calcium level was 3.15 mmol/L. One month post-operatively, this fell to 2.43 mmol/L, which was maintained at 5 and 9 years (2.36 mmol/L and 2.40 mmol/L, respectively; $P < 0.01$). In addition, at 9 years, phosphate levels remained low (1.3 mmol/L), statistically not significantly different from baseline resulting in a calcium–phosphate product of 3.0 $mmol^2/L^2$ (well within the normal range).

The median PTH level was <2 pg/mL on the first post-operative day. It remained low (6 pg/mL) at 1 year, 5 years (10 pg/mL) and 9 years (12 pg/mL) post-operatively ($P < 0.01$).

Table 2 highlights the proportion of patients, at various moments, who had low, normal or high PTH levels. The Chi-squared test was used to confirm statistical significance. A P value less than 0.05 was taken to be significant. One month post-operatively, the majority of patients were hypoparathyroid (18/26 patients, i.e. 69%). This remained the case 1 year post-operatively. At 5 years, less patients were hypoparathyroid (13/26, i.e. 50%). At 9 years, the majority of patients (11/20, i.e. 55%) had a normal PTH level ($P < 0.05$), with only 3 patients exhibiting recurrent hyperparathyroidism.

Discussion

The purpose of this retrospective study was to highlight the long-term outcome of RTx patients with tertiary HPT who underwent total PTX without autotransplantation at our institution. The results demonstrate that total PTX can be protective against recurrent hypercalcaemia in the long-run and represents an effective treatment for persistent HPT after RTX.

Given the fact this series began in 1989, when PTH was not routinely measured immediately post-operatively and with the unavailability of intra-operative PTH level monitoring, it can be postulated that some of these total PTX procedures were in fact subtotal.

Table 1 Median serum levels of calcium, phosphate, creatinine and PTH (range) at different time points

Serum level	Pre-op	1 month PO	6 months PO	1 year PO	5 years PO	9 years PO
Calcium (mmol/L)	3.1	2.41*	2.38*	2.36*	2.40*	2.39*
Phosphate (mmol/L)	1.4	1.2	1.2	1.1	1.2	1.3
Creatinine (μmol/L)	130	145	134	134	126	130
PTH (pg/mL)	321	6 (<2 to 50)*	6 (<2 to 78)*	6 (<2 to 76)*	10 (<2 to 99)*	12 (<2 to 100)*

Pre-op pre-operatively, *PO* post-operatively

* $P < 0.01$(compared to levels pre-op)

Table 2 Proportion of patients with low PTH (<10 pg/mL), normal PTH (10–65 pg/mL) and high PTH (>65 pg/mL) post-operatively

Time from PTX	1 month PO	6 months PO	1 year PO	5 years PO	9 years PO *
Low PTH	18/26 (69%)	18/26 (69%)	18/26 (69%)	13/26 (50%)	6/20 (30%)
Normal PTH	8/26 (31%)	6/26 (23%)	6/26 (23%)	11/26 (42%)	11/20 (55%)
High PTH	0/26 (0%)	2/26 (8%)	2/26 (8%)	2/26 (8%)	3/20 (15%)

PO post-operatively

* $P < 0.05$ (compared to 1 year PO)

However, there are two main factors to support the notion that adequate total PTX procedures were performed. All parathyroidectomies were performed by experienced surgeons, who documented that all visible parathyroid glands were completely removed, and this was confirmed histologically. Secondly, all immediately post-operative PTH levels available were <2 pg/mL. From a nephrological perspective, normocalcaemia (or the absence of recurrent hypercalcaemia) was identified as the primary outcome for a successful PTX. One month post-operatively, 18 patients were hypoparathyroid, as expected following total PTX, with no evidence of recurrent hyperparathyroidism in the entire cohort of patients at 1 month post-operatively. When these patients were analysed independently as representative for the entire cohort (i.e. excluding the eight patients with normal PTH levels at 1 month), the same trend and results were seen. Hence, the data are presented for the entire cohort.

In this series, the mean time post-RTX till PTX was 4 years, as it was sometimes only the later rise in calcium levels which prompted the PTX. Serum creatinine levels were similar pre- and post-operatively and were maintained in the long-run. This is consistent with the findings of Reyes et al. [7]. Perhaps more importantly, the majority of patients (55%) restored normal PTH levels at 9 years (Table 2). The mechanism by which this occurs warrants further evaluation.

Thirty percent of patients remained hypoparathyroid, but, with adequate oral supplementation of 1-α-calcidol (and calcium supplementation when required), they were normocalcaemic. Although these patients had low PTH levels by KDOQI guidelines, there was no diagnosis of adynamic bone disease made, and no bone biopsy was performed. There were no confirmed fractures in this cohort, and calcium levels remained normal at 9 years, with no cases of calciphylaxis, which is the most feared result of adynamic bone disease. However, it must be noted that the clinical diagnosis of some vertebral fractures may be missed. This is important in patients with frank hypoparathyroidism, in which adynamic bone disease is most frequent. No patients presented with symptoms or signs of vertebral fractures.

Fifteen per cent (3 patients) developed recurrent HPT; two of these patients developed normal PTH levels at 1 month and recurrent HPT at 6 months (which persisted at 9 years), and the third patient developed recurrent HPT at 9 years. They may have had an ectopic or supernumerary parathyroid gland that was not removed, perhaps developed de novo primary HPT, or these changes may have only become apparent once the disturbances associated with RTX settled, although this cannot be certain.

Hypercalcaemia is the main manifestation of HPT post-RTX. Its incidence is significant and varies between 8.5 and 65%. The natural evolution of this hypercalcaemia after successful RTX is in most cases to spontaneous resolution [8, 9]. Hypercalcaemia post-RTX is mainly secondary to persistent HPT, although other factors may also play a role, including resolution of soft tissue calcifications, immobilisation, continued high doses of steroid-treatment, and hypophosphataemia [10].

In order to treat patients with persistent or severe HPT and prevent its bone complications, there are mainly two traditional options. The first option is to monitor serum calcium and PTH levels, and intervene when necessary, with an aim to prevent pathologically high levels. The second option involves surgical correction by PTX, which can take the form of total PTX with autotransplantation, subtotal PTX or even total PTX alone. There is, in addition, a third newer option, namely Cinacalcet, which has recently been used [1] and for which there is good evidence in the literature, although it has not been licensed for use in this context.

The optimal surgical procedure for severe secondary HPT has not been fully defined. Most of the recent data in the literature has come from PTX in dialysis patients. Complete removal of all parathyroid tissue has been recommended since the 1960s by several authors [11–13]. In the early 1980s, however, occasional reports commented on severe osteomalacia attributed to hypoparathyroidism post-PTX [14, 15]. It should be noted that uraemia can also contribute to the development of low bone turnover and that aluminium overload can cause osteomalacia and adynamic bone disease. It is thus likely that, during the 1970s and 1980s, such factors may have contributed to the osteomalacia encountered in dialysis patients who underwent PTX. Interestingly, the incidence of aluminium bone disease amongst dialysis patients has declined in the last 15 years, due to the introduction of reverse osmosis and demineralisation techniques. Nevertheless, total PTX without autotransplantation

was abandoned for fear of severe hypocalcaemia and adynamic bone condition, particularly after successful RTX [16, 17]. The preferred surgical strategy focused on removal of most of the parathyroid tissue, with preservation of a small percentage, either by a subtotal cervical PTX or by autografting parathyroid tissue into the forearm.

Patients on dialysis who underwent subtotal PTX or total PTX with autografting have shown high rates of recurrent HPT. Although the reported recurrence rate of HPT is extremely variable, a clear increasing trend is seen with long-term follow-up [18, 19]. This could be due to the disturbances of calcium and phosphate metabolism in the uraemic state that subsequently lead to a constant stimulation of parathyroid tissue. A specific problem of PTX with autograft is an accelerated and tumour-like growth of autotransplanted cells. Higgins et al. [20] reported that after PTX with autotransplantation, every third patient developed symptoms that required re-exploration of the neck or autograft excision. Hampl et al. [21] performed total PTX on 11 haemodialysis patients; their data indicated that treatment with vitamin D3 metabolites and calcium could prevent deleterious bone effects of hypoparathyroidism in this group of patients.

Fewer studies have addressed the treatment of persistent HPT post-RTX. There appears to be no consensus on the optimal surgical technique. Triponez et al. [4] reported a retrospective analysis of 70 patients with tertiary HPT who underwent subtotal PTX with transcervical thymectomy. They concluded that systemic subtotal PTX with thymectomy was effective in treating most RTx recipients with tertiary HPT and also minimised the recurrence of HPT in patients with declining renal function. Triponez et al. [22] also recently reported their retrospective analysis of 74 RTx patients with persistent HPT who underwent limited and subtotal PTX. They suggested RTx patients with tertiary HPT should usually be treated by subtotal parathyroidectomy, as limited PTX was associated with a fivefold increase in risk of persistent or recurrent hyperparathyroidism.

More recently, Drakopoulos et al. [6] reported their experience with total PTX in 12 RTx recipients. Follow-up evaluation showed that calcium homoeostasis was controlled adequately. Rayes et al. [7] reported similar results and found that post-operative calcium and phosphorus normalised in all subjects, which was also associated with markedly decreased bone pain. In those patients who underwent total PTX, there was no evidence of recurrence of HPT but this was not the case with subtotal PTX. The former study concluded that total PTX was the treatment of choice in both subgroups of patients, and the latter concluded that total PTX appears both safe and protective against recurrent and persistent disease, but if subtotal PTX were to be performed, the remnant parathyroid tissue should be small. Table 3 summarises these two studies pertaining to total PTX without autotransplantation for tertiary HPT, in addition to a more recent paper by Coulston et al. [23]. Table 3 thus represents an up-to-date account of the limited published data available on this topic. It was more difficult to establish the biochemical parameters in the latter study, as their data were presented for all PTX patients, of whom the total PTX without autotransplantation cohort was a subgroup of their full analysis. In addition, Gasparri et al. [24] reported their results of total PTX as part of their entire cohort of other forms of PTX in both secondary and tertiary HPT. It was difficult to distil their results for this specific subgroup in question; hence, this study was not included in this table.

Although PTX may be the solution to persistent HPT in RTx patients, some of these patients may be unsuitable surgical candidates. Such patients may present with extensive co-morbidities and surgery contraindications. These candidates may require an alternative to traditional PTX in order to treat their HPT and hypercalcaemia. With the recent advent of cinacalcet into clinical use, there is now the potential to use this drug as an alternative to PTX. It must be noted that calcimimetics have also been reported to produce normocalcaemia in this group of patients [1]. However, currently this is an expensive ongoing therapy, compared to a "one-off" surgical procedure of PTX.

Our study was limited by the small number of patients, its retrospective nature, and the unavailability of pre-operative imaging and intra-operative PTH measurements. However, it is currently the largest retrospective series with the longest follow-up of this specific patient population in the literature. It must be noted, however, that we only looked at the biochemical benefits of total PTX without autotransplantation; a bone-specific measure of its clinical benefit may have been more useful, e.g., fracture rate, densitometry or bone biopsy. This may be an area of future

Table 3 Summary of the literature with regards to total PTX without autotransplantation in tertiary hyperparathyroidism

Author (year)	Rayes et al. [7]	Drakapoulos et al. [6]	Coulston et al. [23]
Type of study	Retrospective	Retrospective	Retrospective
Number of patients	17	12	20
Time to PTX from RTX (months)	23.8	19 ± 8.7	Unclear[a]
Final follow-up (months)	41	25 ± 7.6	1–120[a]
Post-op calcium levels (mmol/L)	2.23 (8.9 mg/dL)	2.31 (9.24 mg/dL)	Unclear (presumably normalised)[a]
Post-op PTH levels (pg/mL)	Undetectable	27.59	Normalised or recurrent[a]
Oral supplementation	Cholecalciferol for all 17 patients. Calcium for 12 patients	Calcium and Vitamin D (mainly 1 α calcidol) for most patients	Cholecalciferol for all patients. Calcium for some patients
Results of total PTX compared to results of	16 RTx patients who underwent subtotal PTX	21 dialysis patients who underwent total PTX	N/A[a]

[a] These patients were part of the entire cohort of 115 patients. This study looked at total PTX without AT of whom the majority had secondary HPT. The breakdown for their 20 RTx patients was not specified. Fourteen of 101 patients developed recurrent HPT; presumably these were dialysis not RTx patients

research and such long-term results would be interesting to follow up.

Conflicts of interest None.

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