Long-term control of parathyroid hormone and calcium-phosphate metabolism after parathyroidectomy in children with chronic kidney disease

Betti Schaefer¹, Katja Schlosser², Elke Wühl¹, Petra Schall¹, Günter Klaus³, Franz Schaefer¹ and Claus Peter Schmitt¹

¹Center for Pediatric and Adolescent Medicine Heidelberg, University of Heidelberg, INF 430, 69120 Heidelberg, Germany, ²Department of Surgery, University of Marburg, Marburg, Germany and ³KfH-Kidney Center for Children and Adolescents, Marburg, Germany

Correspondence and offprint requests to: Claus Peter Schmitt; E-mail: claus.peter.schmitt@med.uni-heidelberg.de

Abstract

Background. Hyperparathyroidism (HPT) is an essential contributor to bone disease and cardiovascular calcifications in children with chronic kidney disease (CKD). Pharmacological and dietary interventions are of limited efficacy; calcimimetics are not yet recommended in children. Parathyroidectomy (PTX) is ultimately performed if HPT becomes refractory to conservative measures; the long-term results and the impact of subsequent kidney transplantation (NTX), however, have not yet been evaluated.

Methods. We analyzed the postsurgical course of 18 paediatric CKD patients with refractory HPT who underwent PTX and autotransplantation of tissue fragments. PTX was successful in all but one patient with an ectopic fifth gland; median follow-up time was 8.3 (range 2.8–19) years.

Results. Parathyroid hormone (PTH) dropped within 1 year after PTX from 1030 ± 108 to 98 ± 18 pg/ml, Ca*P from 59.5 ± 3 to 49 ± 2 mg ²/dl². Oral calcium supply transiently increased from 18.7 ± 4.2 to 24.1 ± 4.8 mg/kg/day within the first 6 months (all P < 0.05). Haemoglobin increased from 10.7 ± 0.4 to 11.5 ± 0.3 g/dl (P < 0.01), despite similar erythropoietin dose and ferritin levels. In patients on long-term dialysis, Ca*P increased again after 18 months; three patients required a second PTX after 3.8, 12 and 12.3 years. Twelve patients underwent NTX 1.8 (0.3–3.8) years after PTX, which decreased mean PTH and Ca*P into the target range throughout the entire post-NTX observation period. Postoperative complications included one transient recurrent nerve palsy, one hypocalcaemic seizure and a case of haemopericardium. At present, no patient has clinical signs of bone disease.

Conclusions. PTX accomplishes long-term control of HPT and calcium-phosphate metabolism in children with CKD and following PTX and may thus mitigate uraemic bone and cardiovascular disease. This has to be taken into account if alternative long-term therapy with calcimimetics (with as yet unknown effects on longitudinal growth and pubertal development) is considered.

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Table 1. Bone and mineral biochemistry and specific medication in 17 children who underwent parathyroidectomy for refractory HPT. Six- to 12-month interval mean values are given. Calcium, cholecalciferol and calcitriol supply reflects mean dosages of treated patients. Three children had a functioning renal graft after 6 and 12 months, six children after 5 years and three children after 10 years. n.s. = not significant

<table>
<thead>
<tr>
<th></th>
<th>6 months prior to PTX</th>
<th>1–6 months post PTX</th>
<th>7–12 months post PTX</th>
<th>5th year post PTX</th>
<th>10th year post PTX</th>
<th>P-value (compared to the 6 months preoperative mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum PTH (pg/ml)</strong></td>
<td>1030 ± 108</td>
<td>137 ± 47</td>
<td>98 ± 18</td>
<td>124 ± 32</td>
<td>375 ± 189</td>
<td>&lt;0.0001, &lt;0.0001, &lt;0.01, &lt;0.001, 0.001, &lt;0.05, &lt;0.05, n.s.</td>
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<tr>
<td><strong>Serum Ca (mg/dl)</strong></td>
<td>10.5 ± 0.2</td>
<td>9.4 ± 0.2</td>
<td>9.5 ± 0.2</td>
<td>9 ± 0.2</td>
<td>8.9 ± 0.2</td>
<td>&lt;0.0001, &lt;0.0001, &lt;0.01, &lt;0.001, 0.001, &lt;0.05</td>
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<tr>
<td><strong>Serum P (mg/dl)</strong></td>
<td>5.7 ± 0.3</td>
<td>4.9 ± 0.2</td>
<td>5.2 ± 0.2</td>
<td>4.9 ± 0.3</td>
<td>5 ± 0.5</td>
<td>&lt;0.05, n.s., n.s., n.s., &lt;0.001, &lt;0.005, &lt;0.05</td>
</tr>
<tr>
<td><strong>Serum Ca<em>p</em> product (mg²/dl²)</strong></td>
<td>59.5 ± 3</td>
<td>45.7 ± 2.1</td>
<td>49.4 ± 1.9</td>
<td>44 ± 2.9</td>
<td>43.9 ± 4.6</td>
<td>&lt;0.05, n.s., &lt;0.005, &lt;0.005, &lt;0.05</td>
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<td><strong>Serum AP (IU)</strong></td>
<td>785 ± 116</td>
<td>529 ± 85</td>
<td>442 ± 91</td>
<td>219 ± 38</td>
<td>175 ± 35</td>
<td>&lt;0.005, &lt;0.005, &lt;0.005, &lt;0.05</td>
</tr>
<tr>
<td><strong>Serum 25(OH)D₃ (nmol/l)</strong></td>
<td>44 ± 6</td>
<td>71 ± 11</td>
<td>61 ± 4</td>
<td>96 ± 23</td>
<td>30 ± 2</td>
<td>all P = n.s.</td>
</tr>
<tr>
<td><strong>Calcium supply (mg/kg/day)</strong></td>
<td>18.7 ± 4.2</td>
<td>24.1 ± 4.8</td>
<td>25.6 ± 7.9</td>
<td>16.7 ± 9.6</td>
<td>7.9 ± 4</td>
<td>&lt;0.05, n.s., &lt;0.05, &lt;0.01</td>
</tr>
<tr>
<td><strong>Cholecalciferol (IU/kg/week)</strong></td>
<td>308 ± 90</td>
<td>314 ± 91</td>
<td>303 ± 90</td>
<td>133 ± 42</td>
<td>203 ± 34</td>
<td>all P = n.s.</td>
</tr>
<tr>
<td><strong>Calcitriol (µg/kg/week)</strong></td>
<td>0.29 ± 0.06</td>
<td>0.24 ± 0.1</td>
<td>0.19 ± 0.09</td>
<td>0.11 ± 0.03</td>
<td>0.05 ± 0.03</td>
<td>n.s., n.s., n.s., n.s.</td>
</tr>
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</table>

After guarded early experience with subtotal PTX, total PTX and subcutaneous autotransplantation of tissue fragments [11] nowadays is the technique of choice in children as it facilitates management in case of HPT recurrence. Two previous reports suggest that the surgical procedure is safe and effective and can be recommended for the treatment of tertiary HPT [12,13]. Detailed assessments of the long-term impact of PTX on parathyroid hormone (PTH) production, mineral metabolism and clinical outcomes are scarce and absent in paediatric populations. Likewise, the impact of kidney transplantation after PTX is unclear. In this work, we provide a comprehensive analysis of the long-term outcome in a series of 18 paediatric patients who underwent PTX due to uraemic HPT refractory to conservative treatment.

Materials and methods

Between 1989 and 2008, 18 paediatric patients with chronic kidney disease underwent PTX for HPT refractory to pharmacological and dietary treatment. Median age at time of operation was 12 ± 6 (range 2–22) years. Two patients were treated and surgery performed at the University Hospital of Marburg; one patient had received a first PTX at Hannover Medical School, Germany and was referred for a second PTX. At the time of PTX, three patients were on conservative treatment with a glomerular filtration rate (GFR) of 10, 11 and 18 ml/min/1.73 m², respectively; seven received peritoneal dialysis, seven haemodialysis and one patient had undergone renal transplantation 26 months prior to PTX. The 14 dialysis patients had received dialysis for 51 (8–137) months. A total of 203 patients were treated in our center by long-term dialysis, i.e. for more than 3 months, between 1989 and 2008. Underlying diagnoses were hypoplastic kidney disease with or without refluxive or obstructive uropathy (n = 8), haemolytic–uraemic syndrome (n = 2), prune belly syndrome (n = 1), nephroptosis (n = 1), steroid-resistant nephrotic syndrome (n = 1) and unknown origin (n = 5). Monthly data were collected as available during the year preceding PTX and the post-PTX period of 99 (33–232) months.

Serum intact PTH, creatinine, calcium, phosphate, alkaline phosphatase, 25-hydroxy vitamin D, albumin, haemoglobin and blood gases were determined using standard methods. Creatinine and urea clearances were measured in 24-h urine collections and GFR calculated as the mean of creatinine and urea clearance. Casual systolic and diastolic blood pressure measurements and the current medications were recorded. Total calcium supply was calculated from the calcium-containing phosphate binders and the oral calcium supplements. X-rays performed within 1 year prior to and after PTX were analyzed with respect to signs of renal osteodystrophy, i.e. demineralization, subperiostal erosions, acneosteolysis, focal radiolucencies and epiphyseal deformation.

Statistics

Data are given as mean ± standard error of the mean. Time-integrated consecutive laboratory findings at 6- and 12-month intervals were compared by repeated measure ANOVA. Individual significances were assessed using the SAS Contrast option or Mann–Whitney rank sum test in case of non-Gaussian distribution. P < 0.05 was accepted as statistically significant.

Results

Preoperative findings

Prior to PTX mean plasma PTH, serum calcium and phosphate and the Ca*p* product were persistently elevated above the Kidney Disease Outcomes Quality Initiative (K/DOQI) target range (Table 1). Within the 1 year prior to PTX, mean serum PTH levels (7–12 months pre-PTX: 759 ± 137 pg/ml; 1–6 months pre-PTX: 1030 ± 108 pg/ml, P < 0.01) and calcitriol dose increased (7–12 months pre-PTX: 0.23 ± 0.05 µg/kg/week, 1–6 months pre-PTX: 0.29 ± 0.06 µg/kg/week, P < 0.05), whereas all other biochemical parameters and blood pressure remained unchanged. Erythropoietin was required in 14 of 17 patients prior to PTX.

Postoperative findings

PTX was successful in all but one patient with a fifth, ectopic gland. She refused a second operation and was thus ex-
cluded from analysis. Intravenous infusion of calcium was required immediately after surgery in all patients and subsequently replaced by oral calcium supplements.

PTX resulted in a marked drop in plasma PTH levels into the target range in seven patients and below the target range in 10 patients within the first postoperative year (Figure 1, Table 1). Serum calcium was persistently reduced compared to baseline. Serum phosphate was reduced within the first 6 months after PTX but slightly increased thereafter. The Ca*P product was persistently reduced after PTX (Table 1) and within the age-specific paediatric target range in 16 out of 17 patients within the first postoperative year. One child had a mean Ca*P product slightly above the target range (59 mg^2/dl^2).

Total daily calcium supply increased postoperatively as compared to the preoperative level but declined in the long run. During the preoperative year, six children were on thrice weekly, 11 on daily oral calcitriol. One patient received i.v. and i.p. calcitriol for 2 months. Postoperatively, all children received daily calcitriol, four patients were switched to thrice weekly calcitriol after 4–28 months. After 1 year, 15 out of 17 still received calcitriol; the dose thereafter steadily declined (Table 1).

Serum haemoglobin levels were significantly higher 1 year postoperatively (11.3 ± 0.4 vs. 10.5 ± 0.4 g/dl, CKD five patients, P < 0.005). Six to 12 months postoperatively, 13 out of the 14 children without renal graft required erythropoietin therapy at a similar dose as preoperatively (174 ± 36 vs. 185 ± 43 IU/kg/week, P = n.s.), erythropoietin resistance index tended to decrease (prior to PTX: 19.8 ± 5.4 vs. 16.4 ± 5.1 IU/kg/week/g per 100 ml, P = n.s.) and serum ferritin remained unchanged.

No PTX-related effects were noted with respect to serum bicarbonate (23.2 ± 0.5 after 1 year vs. 23 ± 0.4 mmol/l prior to PTX), serum albumin (38.3 ± 1 vs. 38.1 ± 0.6 g/l) and systolic (110 ± 5 vs. 106 ± 4 mmHg) and diastolic blood pressures (74 ± 4 vs. 68 ± 4 mmHg, all P = n.s.). In patients with distinct radiological signs of renal osteodystrophy, X-ray findings of the left hand improved within 1 year after PTX.

**Clinical outcome**

Postoperative complications comprised one episode of hypocalcaemic seizure due to noncompliance with oral calcium supplements, a case of haemopericardium in the patient

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**Fig. 1.** Plasma PTH (a) and serum Ca*P product (b) in CKD children without functioning graft, who underwent parathyroidectomy. Mean concentrations from 6- and 12-month intervals (x-axis) were calculated from individual patients; respective means (cross), medians and 25% and 75% intervals are plotted. Arrowheads indicate patients who underwent a second PTX. #P < 0.05 compared to mean values 7–12 months interval prior to PTX. *P < 0.05 compared to the mean values during the last 6 months prior to PTX.

**Fig. 2.** Plasma PTH (a) and serum Ca*P product (b) in children who underwent PTX and subsequent NTX. Mean concentrations prior to PTX and at time of NTX as well as respective postoperative nadirs and concentrations at the time of last follow-up are given on the y-axis. X-axis indicates the time intervals to PTX, horizontal and vertical error bars indicate time and concentration SEM, respectively. #P < 0.05 compared to mean values 7–12 months interval prior to PTX. *P < 0.05 compared to the mean values during the last 6 months prior to PTX.
with a thoracic adenoma, which required a paracentesis, and a bilateral vocal cord palsy, which largely resolved within 2 months. Five children postoperatively reported reduced bone pain. One 3-year-old boy with multiple slipped epiphyses experienced profound improvement of radiological findings and of physical abilities within 1 year after PTX. At present, no patient has clinical signs of bone disease, e.g., no patient complained about bone or muscle pain or suffered from fractures or bone-related physical disablement.

Impact of renal replacement therapy
Four patients never underwent successful kidney transplantation; one patient returned to haemodialysis 5 years after PTX. PTX resulted in a sustained control of plasma PTH levels, while the effect on Ca*P was less persistent. Three patients subsequently required a second PTX 3.8, 12 and 12.3 years after the first operation (Figure 1). The first patient underwent subtotal excision of the parathyroid autograft; the second patient, who had returned to dialysis 5 years after PTX, required excision of a cervical adenoma. Postoperatively, PTH was again low in both patients. The third patient with slipped epiphyses during infancy had adequate PTH and Ca*P control for more than 12 years after PTX. At that time, a mediastinal adenoma was suggested from the magnetic resonance imaging (MRI) and Mibi scans, which however could not be excised in toto.

Twelve out of 17 patients underwent successful kidney transplantation 22 (3–45) months after PTX. Mean postoperative serum creatinine was 1.42 (0.43–2.30) mg/dl within the first 6 months. NTX resulted in a significant reduction in plasma PTH and Ca*P (Figure 2). PTH decreased to a nadir of 18 ± 27% ($P < 0.05$) and increased again to 67 ± 56% until last observation ($P < 0.05$ compared to nadir, $P = n.s.$ compared to PTH at time of NTX). Serum Ca*P product decreased to a nadir of 59 ± 5% ($P < 0.001$) and increased again to 76 ± 6% until last observation ($P < 0.001$ compared to nadir, $P < 0.01$ compared to Ca*P at time of NTX). Mean Ca*P did not exceed the target range throughout the entire post NTX observation period.

Discussion
CKD mineral and bone disorder in childhood-onset chronic renal failure has recently attained particular attention as a major cause of physical disablement and cardiovascular morbidity in early adulthood [1,16]. Several studies have demonstrated close correlations of the cumulative PTH, calcium and phosphate load with coronary artery calcifications, carotid intima media thickness and cardiovascular mortality [1,2,17–19]. Thus, optimal control of bone and mineral metabolism is mandatory to improve long-term prognosis of paediatric CKD patients. This analysis of monthly collected data demonstrates that total PTX with autotransplantation of parathyroid tissue fragments allows for excellent long-term control of PTH and mineral metabolism in children with HPT refractory to conservative measures. Subsequent NTX results in an additional and persistent decline in PTH and Ca*P into the individual, CKD-specific target range.

Two previous paediatric studies indicated a substantial improvement of clinical and radiological signs of bone disease [12,13], which could now be reconfirmed. These studies however did not analyze the outcome regarding the time-averaged long-term control of PTH and mineral metabolism after PTX and the impact of NTX. Based on monthly data follow-up, we were able to demonstrate a sustained reduction in the cumulative PTH, calcium and phosphate load over more than one decade in most of our patients. After 1 year almost 60%, and after 5 years still 23%, of our children had PTH levels even below the target range. This is still a lower frequency of hypoparathyroidism as reported previously in adults [20]; the clinical implications are as yet unclear. Hypoparathyroidism should particularly promote calcium influx into the bone; impairment of growth is unlikely [21]. Based on our findings, a long-term cardiovascular benefit of PTX in paediatric CKD patients is likely but still needs to be proven. Experimental studies support a permissive role of PTH for cardiac fibrosis, apoptosis and inflammation, which can be abrogated by PTX [22–24]. Clinical observations in adult CKD patients suggest that PTX may prevent or even reverse extrasosseous calcifications [25–27] and improve left ventricular morphology and function [28–30].

After successful NTX, PTH levels usually drop markedly, even in the presence of parathyroid adenoma. In the majority of patients, however, NTX without prior PTX does not normalize PTH plasma levels [10,31]. Persistent HPT after NTX, even if mild, tends to aggravate post-transplant bone disease [32]. PTX performed after NTX has been associated with acute and chronic deterioration of graft function [33–35], partially explained by PTH effects on renal perfusion and glomerular filtration rate [36]. The majority of our patients underwent subsequent NTX nearly 2 years after PTX. At the time of NTX, mean PTH was slightly below the target range and the serum Ca*P product in the normal range. NTX following PTX had a marked additional lowering effect on plasma PTH and the serum Ca*P product. Mean PTH and Ca*P product remained in the target range for the entire post-NTX observation period of up to 11 years. Thus, the combination of PTX and subsequent NTX may be particularly beneficial and should not only prevent cardiovascular sequelae but also improve bone mineral density [37].

In children who remain on haemodialysis, however, adenomatous transformation of the residual or autotransplanted parathyroid tissue and autonomous hyperparathyroidism is likely to develop again. Three out of five of our children who could not successfully be transplanted or had to return to haemodialysis required a second PTX 4–12 years after the first one. This was again successful in two of them but not in the child with a suspected mediastinal adenoma. Whether the calcitriol administration mode, daily or intermittent, had an impact on the control of HPT and the incidence of PTX cannot be concluded from our study; two studies in CKD children demonstrated neither a difference in control of hyperparathyroidism, plasma calcium and phosphate nor an effect on growth rate [3,38].
PTX in children is a technically demanding procedure which requires significant surgical experience [13]. Surgical complications in the present study comprised one case of haemopericardium in an adolescent who underwent extended exploration for an ectopic parathyroid adenoma and vocal cord palsy. In only one girl, hyperparathyroidism persisted, albeit at a lower level. All other children postoperatively developed a marked decline in plasma PTH into or below the target range and symptoms of ‘hungry bone’ necessitating immediate calcium infusions and subsequent continued oral calcium supplementation. This is explained by the extensive HPT and the associated, protracted calcium efflux from bone, whereas in fact a positive bone calcium balance is required in growing children. The increased oral calcium supplementation in the subsequent course reflects the continued remineralization of the skeleton after successful PTX. The gradual rebound of the serum calcium-phosphate product observed 2–3 years after PTX in children without a functioning renal graft coincides with skeletal calcium saturation.

Several additional beneficial effects of PTX beyond control of HPT and mineral homeostasis have been reported in adults. These include improved anaemia with reduced erythropoietin dose requirements [39–41] and, in some but not all studies, lowered arterial blood pressure [41–45]. Data from children are scant. We observed a post-PTX increase in haemoglobin levels, which became significant within 12 months. Potential mechanisms include regression of HPT-induced bone marrow fibrosis with improved red blood cell production and survival, increased endogenous erythropoietin release and improved EPO sensitivity [46]. The latter however was not significantly improved in our patient group.

We did not observe any effect of PTX on casual blood pressure, unlike Goldsmith et al., who observed a significant decrease in 24-h systolic blood pressure in correlation with the decline in serum calcium 9 months after PTX [42], and to the study by Coen et al., who found a reduction in 24-h ambulatory blood pressure monitoring 6, 24 and 60 months post PTX in patients with preoperative hypertension [41].

Calcimimetics are a potential pharmacological alternative to PTX. In adult dialysis patients with secondary HPT, cinacalcet effectively reduced serum PTH for up to 3 years without increasing the serum Ca*P product [47,48]. Cinacalcet has not been tested systematically in children to date, and its use is not yet recommended [15]. Still, it is increasingly used in children with otherwise uncontrolled HPT. Specific paediatric concerns regarding the use of cinacalcet relate to its effects on growth plate chondrocyte proliferation and differentiation [6] and on sex steroid hormone production [49]. They have to be counterbalanced against the surgical risks of PTX and the excellent postoperative control of PTH and mineral metabolism. While animal studies did not reveal a negative impact of cinacalcet on longitudinal growth [7], a recently reported case of a 5-year-old boy who developed precocious puberty coincident with cinacalcet administration, however, warrants caution [50].

In conclusion, parathyroidectomy with autotransplantation of parathyroid tissue allows for excellent long-term control of hyperparathyroidism and calcium-phosphate metabolism in children with CKD, in particular in combination with NTX, and may thus improve uraemic bone disease and mitigate cardiovascular sequelae.

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Conflict of interest statement. None declared.

References

17. De Boer IH, Gorodetskaya I, Young B, Hsu CY, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insuffi-
Parathyroidectomy in children with CKD


49. EMEA. European Assessment Report MIMP ARA. Available at: http://wwwemeaeuropaeu/humandocs/PFDs/EPAR/mimpara/12029804enpdf