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Increase in Bone Mineral Density after Successful Parathyroidectomy for Tertiary Hyperparathyroidism after Renal Transplantation

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Abstract

Background Few studies have reported changes of bone mineral density (BMD) after parathyroidectomy in patients with persistent hyperparathyroidism after renal transplantation (3 HPT).

Patients and Methods We retrospectively analyzed 14 patients who underwent successful parathyroidectomy for 3 HPT and who had available BMD data before and after parathyroidectomy.

Results Median follow-up time was 26 months (IQR: 16.8–40.2). Serum calcium levels decreased significantly after parathyroidectomy (2.32 ± 0.09 versus 2.66 ± 0.16 mmol/l; $p < 0.01$), as did PTH levels (5.1 ± 3.0 versus 27.8 ± 23.7 pmol/l; $p < 0.01$). Nine patients (64%) had a steroid-free immunosuppression at follow-up. Mean increase in BMD was 9.5 ± 8.0% for the spine and 9.5 ± 7.9% for the hip ($p < 0.01$ for both sites). Patients with osteoporosis (T-score ≤ 2.5) or osteopenia (T-score ≤ 1) before parathyroidectomy had the biggest increase in BMD (10.7 ± 7.7% in hip BMD and of 12.3 ± 8.1% in spine BMD).

Conclusions Parathyroidectomy is an efficient treatment of osteoporosis and osteopenia in patients with 3 HPT.

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Introduction

Chronic renal failure (CRF) is associated with a cascade of events affecting mineral metabolism and leading to renal osteodystrophy. In CRF, the deficient production of calcitriol by the kidney and the bone resistance to PTH action lead to hypocalcemia. Phosphorus retention due to the decreased filtration rate and hypocalcemia are both a strong stimulus to the parathyroid glands, leading to an increased proliferation of parathyroid cells and an increased PTH secretion called "secondary hyperparathyroidism." Secondary hyperparathyroidism in CRF leads to osteitis fibrosa cystica and osteopenia [1–3].

Tertiary hyperparathyroidism after renal transplantation (3 HPT) is defined as persistent hypercalcemia after successful renal transplantation and can be observed with an incidence of 30 to 50 percent [4, 5]. However, in most patients, the hypercalcemia resolves in a few months, and only a few percent of patients will need parathyroidectomy [5, 6]. The mechanism of refractory PTH hypersecretion after renal transplantation is due in part to a too high parathyroid cell mass, leading to an inappropriately high basal PTH secretion (diffuse parathyroid hyperplasia); it may also result from parathyroid adenomas that have developed during the course of secondary HPT (nodular

hyperplasia), with parathyroid cells having an abnormal PTH secretion curve in response to calcium [7]. The high PTH levels lead to increased renal tubular reabsorption of calcium and to increased bone resorption, both mechanisms causing hypercalcemia.

In the course of renal failure, the bone becomes resistant to the action of PTH, one of the leading causes of hypocalcemia in secondary HPT. After renal transplantation, the bone recovers its sensitivity to PTH, and the high PTH levels found in 3 HPT after renal transplantation lead to an accelerated bone turnover and then to a rapid loss of bone mass [8]. Immunosuppressive therapy also leads to bone loss; corticosteroids reduce bone formation and increase bone resorption [9, 10], and calcineurin inhibitors (cyclosporine and tacrolimus) induce osteopenia [8]. The fall in bone mass density (BMD) is more consistent during the first post-transplant months, with a rate of bone loss of 1.6% per month during the first 5 months, and it usually continues after that period but at a slower rate [8, 11].

In case of persisting 3 HPT after renal transplantation, the only effective treatment is parathyroidectomy, which corrects the calcium levels in more than 80% of the patients in the long term in experienced centers [12–15]. However, the long-term effect on bone mass has rarely been reported. Therefore, the aim of this retrospective study was to evaluate the effect of parathyroidectomy on BMD in patients with 3 HPT after renal transplantation.

Patients and method

From October 1992 to October 2005, 19 patients underwent parathyroidectomy at the University Hospital of Geneva (15 patients) and at Sankt-Gallen KantonsSpital, Sankt-Gallen, Switzerland (4 patients) for 3 HPT, defined as 2 HPT that did not regress after successful renal transplantation. Among these 19 patients, 5 were excluded from our study; 2 because of persistent 3 HPT after surgery (one had a missed fourth gland and was successfully reoperated after the end of this study and the other had a subtotal parathyroidectomy and is currently under medical treatment), 2 died prematurely of a nonsurgical etiology without enough follow-up, and 1 was lost to follow-up. Patients were transplanted between 1986 and 2004. The immunosuppression regimen varied among the different timing of transplantation, but most of the patients were on a cyclosporin, mycophenolate mofetil, and steroid regimen begun immediately after transplantation. Induction with IL2-R (Basiliximab) was used beginning in 2000. Steroids were withdrawn when possible. All patients were followed from the initiation of dialysis by a team of nephrologists, transplant surgeons, and bone specialists. All patients received appropriate calcium and vitamin D supplementation before parathyroidectomy (according to the serum and urinary calcium levels) and after parathyroidectomy. All patients with osteoporosis received bisphosphonates during the first year after transplantation.

The criteria for surgery were persistent hypercalcemia (calcium level greater than 2.6 mmol/l) with a raised PTH concentration (PTH level greater than 6.8 pmol/l) usually longer than 1 year after kidney transplantation. The procedure was an intended subtotal parathyroidectomy, which is defined as bilateral neck parathyroid exploration, leaving a remnant the size of two normal parathyroid glands.

Outcomes were based on review of the surgery, nephrology, and bone disease specialist case records, including demographic data, history of end-stage renal disease, cumulative dose of corticoid, and pre- and postoperative values of patients' weight, serum creatinine, calcium, and PTH. The two biological markers used in Geneva only to evaluate bone turnover were serum osteocalcin and the ratio of urinary D-pyridinolin/creatinin for formation and resorption, respectively. Bone mineral density values at the lumbar spine (L1–L4) and proximal femur were measured with dual energy x-ray absorptiometry the year before parathyroidectomy and regularly thereafter to assess the effects of medical and surgical treatments. Different measurements in each patient were performed with the same machine. At both sites, BMD is expressed in T-scores, which is the number of standard deviation (SD) between the measured values and the mean BMD for a control group composed of patient with same gender, aged from 25 to 35. Therefore definitions of normal, osteopenic, and osteoporotic patients are, respectively, ≥ -1 SD, -1 to -2.5 SD, and < -2.5 SD. Glomerular filtration rate (GFR) was calculated using the Cockroft and Gault formula [16]. The cumulated dose of corticoid is in prednisone equivalent. It is calculated from the first renal graft and included the loading dose, the graft rejection dose, and the everyday dose.

Statistical analysis

Parameters with normal distribution are expressed as mean $\pm$ SD. Parameters with skewed distribution are expressed as median and interquartile range (IQR). Statistical analysis was performed with SPSS software (SPSS, Chicago, IL). Comparisons between preoperative and postoperative values of BMD, T-score, serum calcium, serum PTH, serum osteocalcin, urinary D-pyridinolin/creatinin, and GFR were made with a paired *t*-test. A value of $p < 0.05$ was considered statistically significant.

Results

Fourteen patients (7 males, 7 females) underwent successful parathyroidectomy for 3 HPT after renal transplantation.

Age at parathyroidectomy was 50.0 ± 10.1 years. Delay from first dialysis to renal transplantation was 27 months (IQR: 6.0–68.2). Two patients experienced failure of a first kidney graft and underwent, respectively, two and three renal transplantations before parathyroidectomy. Delay from last transplantation to parathyroidectomy was 19 months (IQR: 9.8–55.2). Cumulated prednisone dose at parathyroidectomy was 7.2g (IQR: 4.3–22.9). Twelve patients had subtotal parathyroidectomy, one patient had total parathyroidectomy with autotransplantation, and one patient needed three operations to have PTH in the normal range: he first underwent an intended total parathyroidectomy at another medical center for 2 HPT while on dialysis. He was referred to our center after recurrence of 2 HPT, and he underwent a selective right inferior parathyroidectomy, according to the concordant results of preoperative sestamibi scan and ultrasound. After kidney transplantation, he presented persistent/recurrent HPT and underwent a selective left inferior parathyroidectomy, at which a 270 mg hyperplastic parathyroid gland was removed. There were no perioperative deaths in our series. One patient has persistent hypoparathyroidism and is receiving calcium and vitamin D substitution. Laryngoscopy was not routinely performed, but no patient had postoperative dysphonia. Preoperative and follow-up characteristics of the patients are summarized in Table 1.

Follow-up time was 26 months (IQR: 16.8–40.2) after parathyroidectomy. No patient was hypercalcemic at follow-up, and all patients had PTH in the recommended target range according to renal function [1]. Nine patients (64%) had a steroid-free immunosuppression regimen, two patients had 2.5 mg of prednisone, one patient 5 mg and two patients 7.5 mg at follow-up. One patient had only measurement of preoperative spine BMD; all others had pre- and postoperative hip and spine BMD measurements. Patients had two to five BMD measurements during follow-up according to length of follow-up.

All patients increased their hip BMD, except one who decreased it by 2% and who had the highest preoperative BMD (Fig. 1). Similarly, all patients increased their spine BMD except one, who decreased it by 5% (Fig. 2) Mean increase in BMD was 9.5 ± 8.0% for the spine and 9.5 ± 7.9% for the hip, corresponding to a mean yearly increase of 3.8 ± 3.3% for the spine and 4.3 ± 4.8% for the hip. Patients with significant bone loss preoperatively (osteoporosis or osteopenia, T-score ≤ 1) had an increase of 10.7 ± 7.7% in hip BMD and of 12.3 ± 8.1% in spine BMD. Before parathyroidectomy, 2 patients were osteoporotic at the spine and 3 at the hip, and six were osteopenic at the spine and 8 at the hip. At follow-up, no patient was osteoporotic, either at the spine or at the hip, and three were osteopenic at the spine and 7 at the hip. All sites combined, 5 patients changed from osteoporosis to osteopenia and 8 from osteopenia to normal BMD. Patients with more BMD loss (worse T-score) had the biggest increase in BMD (Fig. 3). The increase in BMD was higher in patients without steroids at follow-up; however, the difference was not significant, possibly because of the small sample size (10.1 ± 8.9% versus 8.5 ± 6.8% for the spine and 10.2 ± 4.9% versus 8.2 ± 11.9% for the hip). Similarily, a decrease in serum osteocalcin and urinary D-pyridinolin/creatinin ratio suggested a decrease in bone turnover. However, these changes were statistically not significant.

Discussion

The aim of this retrospective study of patients with 3 HPT after renal transplantation was to investigate the effect of parathyroidectomy on BMD. We found that parathyroidectomy significantly increased postoperative BMD in 25 of 27 sites studied in 14 patients.

Table 1 Preoperative and follow-up characteristics of patients undergoing parathyroidectomy for 3HPT after renal transplantation

Characteristics	Preoperative	Follow-up	*p* Values
Serum calcium level (mmol/l) (ref 2.2–2.52)	2.66 ± 0.16	2.32 ± 0.09	<0.001
Serum PTH level (pmol/l) (ref 1.1 - 6.8)	27.8 ± 23.7	5.1 ± 3.0	0.004
GFR (ml/min)	67.6 ± 23.5	59.2 ± 28.0	0.094
Serum osteocalcin (g/l) (N = 7)	31.5 ± 18.9	23.1 ± 18.2	0.59
Urinary D-pyridinolin/creatinin (nmol/mmol) (N = 7)	12.4 ± 3.9	9.1 ± 2.8	0.234
BMD at spine (g/cm^2)	0.977 ± 0.176	1.061 ± 0.146	<0.001
BMD at proximal femur (g/cm^2)	0.748 ± 0.124	0.825 ± 0.125	0.002
T-score at spine (SD)	−1.0 ± 1.4	−0.3 ± 1.1	
T-score at proximal femur (SD)	−1.8 ± 0.8	−1.1 ± 0.8	

GFR glomerular filtration rate; BMD bone mass density; *ref* reference range

Results are mean ± SD

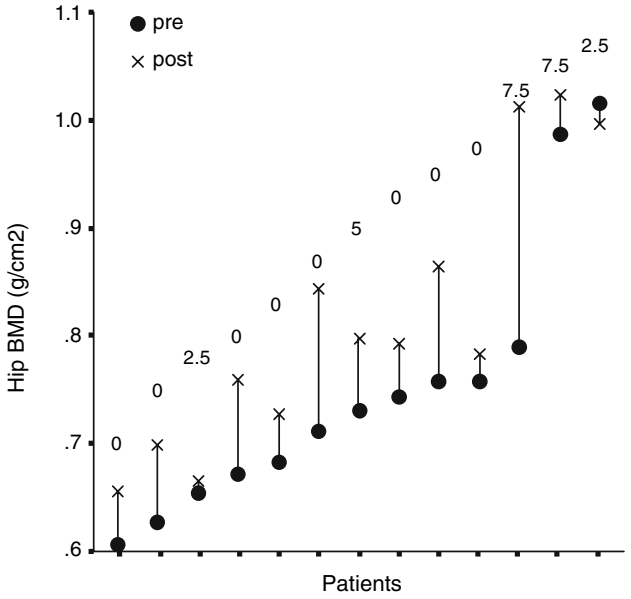

Fig. 1 Change in bone mineral density (BMD) of the hip for each patient, sorted from lowest to highest preoperative value. Pre: preoperative, post: follow-up. The dose of prednisone at follow-up is indicated for each patient

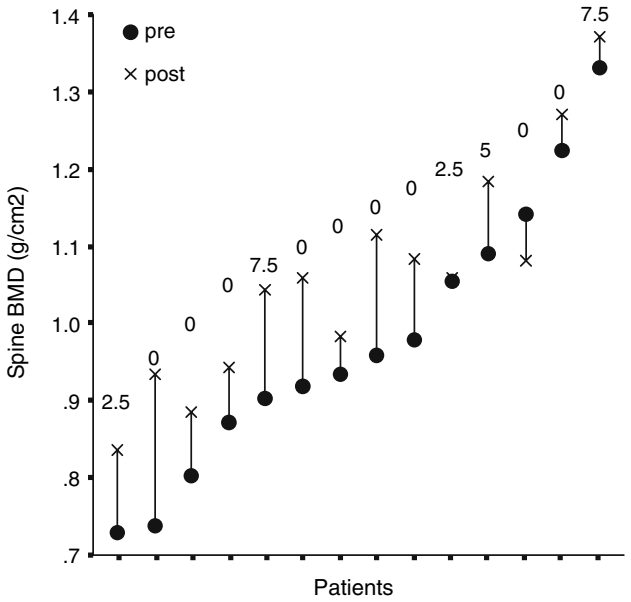

Fig. 2 Change in BMD of the spine for each patient, sorted from lowest to highest preoperative value. Pre: preoperative, post: follow-up. The dose of prednisone at follow-up is indicated for each patient

Among 19 patients who underwent surgery for 3 HPT after renal transplantation in both centers, one patient was lost to follow-up and 2 were excluded because of persistent/recurrent HPT. Therefore, parathyroidectomy was effective in normalizing calcium and PTH levels in 16 of 18 patients (89%), similar to the long-term cure rate of 70%–100% reported in other series, the difference in cure

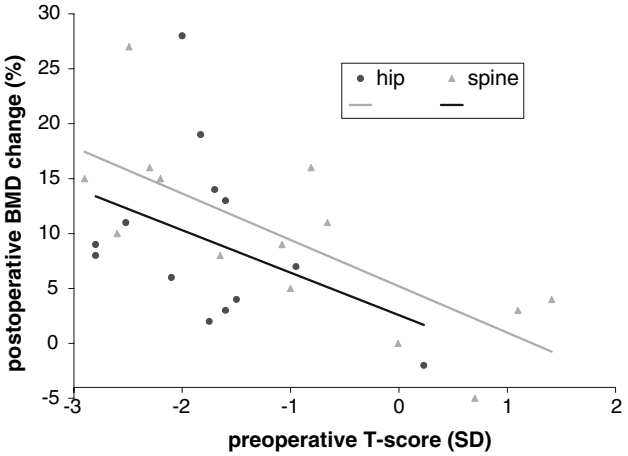

Fig. 3 Correlation between preoperative T-score and percent change in BMD. R^2 for the hip = 0.5; R^2 for the spine = 0.15

rate being mainly due to the different criteria used [12–15, 17–19].

Very few studies on parathyroidectomy for tertiary hyperparathyroidism after renal transplantation have reported the long-term effect on bone mass, although some have reported the change in total alkaline phosphatase. In the study by Seehofer et al., the results are given for secondary and tertiary patients together [20]. Sitges-Serra and Caralps-Riera reported a decrease from 186 ± 153 IU/l to 77 ± 33 IU/l [21], and Nichol et al. reported a decrease from 195.9 U/l to 94.7 U/l [13].

One study, by Abdelhadi and Nordenstrom, on bone recovery after parathyroidectomy in patients with primary and renal hyperparathyroidism (patients on dialysis and patients after renal transplantation) reported an "only marginal increase" in BMD after parathyroidectomy in patients with 3 HPT [22]. Data taken from the graph show that total body, lumbar spine, and femoral neck BMD increased by about 2.1 ± 1.1%, 4.4 ± 2.1%, and 2.2 ± 3.3% (mean ± sem), 3 years after parathyroidectomy in 11 patients. In their study, published in 1998, all kidney transplant recipients (transplanted between 1977 and 1992) were on a corticoid based immunosuppression (prednisolone, cyclosporine, and/or azathioprine), ate a normal diet (probably no calcium supplementation), and none of them received vitamin D supplementation.

Milas and Weber showed a mean increase of 7.1 ± 6.4% in bone mass density of the hip, lumbar spine, and forearm 23 ± 25 months after parathyroidectomy in a subgroup of 16 patients with available pre- and postoperative data, among 36 patients with tertiary hyperparathyroidism. The date of kidney transplantation is not mentioned is this subgroup of patients but, according to the follow-up time, patients most likely received transplants after 1995 [23].

The present study shows an increase in BMD by 9.5 ± 8.0% at the spine and 9.5 ± 7.9% at the hip after a median follow-up of 26 months after parathyroidectomy. The BMD increased less in the study by Abdelhadi and Nordenstrom, and there are different possible reasons for that. First, their study is older than the two other. Therefore, most of their patients probably did not receive a bone-sparing immunosuppression regimen, as currently recommended [1, 24]. The detrimental effects of long-term immunosuppression, and particularly of corticoid therapy, on bone mass is well established [8, 25–27], and, because of prolonged survival after kidney transplantation, more interest is now given to bone metabolism. In our study, one patient was transplanted in 1986, the 13 others between 1996 and 2004. All of them had the lowest possible dose of steroids, as demonstrated by the fact that 64% of them had a steroid-free regimen at follow-up, compared to none of their patients. Moreover, among different possible interventions to prevent bone loss after transplantation, vitamin D supplementation has consistently demonstrated its efficacy [27] and is currently recommended after renal transplantation [1, 24, 27]. No patient in the study by Abdelhadi and Nordenstrom received calcium and vitamin D supplementation, whereas all patients in our study received both. Second, the three studies were small (14 patients in ours, 16 in the study by Milas et al., and 13 at 2 years and 11 at 3 years in the study by Abdelhadi and Nordenstrom), and the differences might not be statistically significant. Third, the preoperative bone mass density is not mentioned for the hip and spine in the subset of patients with 3 HPT in the study by Abdelhadi and Nordenstrom, and it may be that patients in the study by Milas et al. and in our study had more advanced bone loss than their patients. In effect, BMD increases more in patients and at sites with lowest preoperative T-score, as also reported in previous studies in primary and renal hyperparathyroidism [22, 28].

Previous studies reported some BMD increase after the immediate post-transplant period in some patients [4, 29]; however, the increase was never more than a few percent. The > 9% increase shown in the present study suggests that it does not only occur as a result of spontaneous bone change after better medical management. As all our patients were followed by the same team from the time of dialysis, it is anticipated that the medical treatment was already the best possible before parathyroidectomy.

After parathyroidectomy for primary hyperparathyroidism, the reported increase in BMD ranges between 3.2% and 12.2% in different studies according to follow-up times and severity of bone loss preoperatively [28, 30–32]. Our study showing an increase of 9%–10% in hip and spine BMD suggests that, in 3 HPT after renal transplantation, results at least as good as those obtained in primary hyperparathyroidism can be expected. This contrasts with the hypothesis of Abdelhadi and Nordenstrom [22], who suggested that performing a parathyroidectomy on kidney transplant recipients could be too late from a bone-preserving perspective.

Calcimimetics have been recently developed and may offer an interesting alternative to parathyroidectomy in patients with 3 HPT after renal transplantation in the future. However, they are not currently approved for the treatment of 3 HPT in most countries, leaving parathyroidectomy as the single option. The obligatory cessation of calcimimetics after renal transplanation might lead to rebound hyperparathyroidism and, while a decrease in the prevalence of parathyroidectomy is currently seen in 2 HPT patients, an increase in the need for parathyroidectomy in 3 HPT patients is anticipated by some authors [6]. Three recent series reported the use of Cinacalcet in kidney transplant recipients [33–35]. All of them demonstrated its efficacy in normalizing serum calcium level and its safety on graft function. However, one study did not show any change in PTH level [33], and the other two showed only minimal decrease of PTH level (171 versus 148 pg/ml [35] and 176 versus 135 pg/ml [34], before and after treatment, respectively). Bone mineral density and bone markers were not studied in these short-term studies (maximum 6 months). In primary hyperparathyroidism, calcimimetics were similarly effective in normalizing serum calcium levels; only slightly decreased PTH levels, however, did not change BMD after 1 year [36], nor after 5 years. The effects of calcimimetics on BMD in patients with 3 HPT after transplantation are still awaited.

This study has several limitations; first, it is retrospective and therefore BMD analysis and blood and urine sampling occurred at different time points after parathyroidectomy. However, the consistent increase in BMD postoperatively suggests that this increase persists over time, as previously demonstrated for primary hyperparathyroidism [32]. Apart from small sample size, the nonstandardized timing of blood and urine sampling might be the reason for the nonsignificant difference in bone markers pre- versus postoperatively. Second, the sample size is small and heterogeneous in terms of patient characteristics such as age, sex, kidney function, delay between kidney transplantation and parathyroidectomy, not allowing subset analysis of patients who would benefit more from parathyroidectomy. Whether the BMD would increase more after parathyroidectomy by waiting until the patient reaches a baseline immunosuppression, if possible steroid free, or whether the BMD would increase more if parathyroidectomy were performed as early as possible once the persistence of 3 HPT has been demonstrated, is an important issue that needs further study.Third, the different impact of the different procedures (parathyroidectomy,

steroid withdrawal, calcium and vitamin D supplementation) on BMD changes cannot be elucidated from this study.

Conclusions

Subtotal parathyroidectomy is a safe and efficient treatment to correct the calcium and PTH levels and to increase BMD in patients with 3 HPT after renal transplantation. In the present study, parathyroidectomy combined with bone-preserving immunosuppression and calcium and vitamin D supplementation led to a >10% increase of BMD in patients with osteoporosis or osteopenia 2.2 years after parathyroidectomy. Whether calcimimetics will have a different impact on bone mineral density remains to be investigated; however, so far, only parathyroidectomy has been demonstrated to have such a beneficial effect on BMD. Further studies are needed to show whether early parathyroidectomy (3 months after renal transplantation has been suggested by some authors [6]) could avoid severe loss of BMD after renal transplantation. We therefore recommend parathyroidectomy in patients with 3 HPT after renal transplantation and reduced bone mass density.

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