ORIGINAL ARTICLE

Parathyroidectomy Can Improve Bone Mineral Density in Patients With Symptomatic Secondary Hyperparathyroidism

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Hypothesis: The recovery of osteoporosis or bone mineral density (BMD) after parathyroidectomy and autotransplantation can be improved in patients with symptomatic secondary hyperparathyroidism.

Design: Case series.

Setting: Tertiary referral center.

Patients: Forty-five patients with symptomatic secondary hyperparathyroidism who underwent total parathyroidectomy and autotransplantation were included. They were divided into an osteoporotic group (n=20) and a nonosteoporotic group (n=25) according to preoperative T scores less than –2.5 at either the lumbar spine (L1-L4) or the femoral neck (FN).

Interventions: Serum levels of calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone were checked before surgery and 1 day, 1 week, and 3 months after surgery. The BMDs of the FN and L1-L4 were measured using dual-energy x-ray absorptiometry before surgery and 6 months after surgery.

Results: Patients with osteoporosis were older (mean±SD, 50.2±14.0 years) than those without osteoporosis (42.7±9.1 years) (P=.04). Except for bone fractures found in 2 women in the osteoporotic group, there were no significant differences between the 2 groups in sex, clinical manifestations, duration of dialysis, weight of removed parathyroid tissue, and types of dialysis. Also, serum levels of calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone were similar in both groups. Both 1 day and 1 week after total parathyroidectomy and autotransplantation, serum levels of calcium and intact parathyroid hormone decreased rapidly and then gradually increased 3 months later; however, serum levels of alkaline phosphatase increased rapidly and then gradually decreased 3 months later. Six months after parathyroidectomy, BMD, T score, and Z score at L1-L4 and the FN increased significantly ($P<.001$). The increment was much better in the osteoporotic group than in the nonosteoporotic group ($P<.001$). Also, osteopenia or osteoporosis improved significantly after parathyroidectomy at both L1-L4 and the FN ($P<.001$ for both).

Conclusion: Parathyroidectomy and autotransplantation can improve BMD of symptomatic secondary hyperparathyroidism at L1-L4 and the FN.

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RENAL osteodystrophy is a well-recognized complication in adults with end-stage renal failure undergoing maintenance hemodialysis and is associated with marked morbidity. Osteitis fibrosa with variable associated osteosclerosis, caused by elevated levels of circulating parathyroid hormone, is the most consistent histological abnormality and might be associated with osteopenia and osteoporosis.[1] Traditionally, severe bone pain, pruritus, general weakness, and extensive soft tissue calcification are indications for parathyroidectomy in secondary hyperparathyroidism.[2-6] In this study, we sought to determine the differences in clinical manifestations between patients with and without osteoporosis and to assess the recovery of bone mineral density (BMD) or osteoporosis after surgery.

RESULTS

The causes of renal failure were chronic glomerulonephritis in 24 patients, chronic pyelonephritis in 3, diabetic nephropathy in 2, hypertensive nephropathy in 1, obstructive uropathy in 1, polycystic kidney in 1, and idiopathic nephropathy in 13. Diabetes mellitus was found in the osteoporotic group only (2 of 20 patients). The clinical manifestations of the 45 patients were bone pain, pruritus, general weakness, soft tissue calcification, etc. There were no significant differences be-

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PATIENTS AND METHODS

Between July 1, 1996, and December 31, 1999, 45 patients with symptomatic secondary hyperparathyroidism who underwent total parathyroidectomy and autotransplantation of 60 mg of subcutaneous tissue,[7] no matter how many parathyroid glands were found during surgery, were enrolled in this study. Clinical manifestations were recorded in the medical chart. Routinely, patients undergoing regular dialysis took calcium carbonate or acetate as a phosphate binder. The ordinary dialysate contained a calcium level of 28.00 mg/dL (7.0 mmol/L) using either hemodialysis or peritoneal dialysis. Vitamin D_3 was prescribed if serum levels of intact parathyroid hormone (iPTH) had been more than 3 times normal (>199 pg/mL [21 pmol/L]), and intravenous vitamin D_3 was given if serum levels of iPTH had been greater than 997 pg/mL (105 pmol/L). Symptomatic patients such as those with bone pain, pruritus, general weakness with disability, etc, who had normal levels of aluminum and iPTH levels greater than 10 times normal (>649 pg/mL [68.3 pmol/L]) despite the vitamin D_3 suppressive treatment were referred to surgical intervention. Before surgery, levels of calcium, phosphorus, alkaline phosphatase, and iPTH and BMD were checked routinely. One day, 1 week, and 3 months after parathyroidectomy, calcium, phosphorus, alkaline phosphatase, and iPTH levels were checked again. The BMD was reexamined 6 months after surgery. The BMD of the femoral neck (FN) and lumbar spine (L1-L4) was measured using dual-energy x-ray absorptiometry (model QDR-4500; Hologic Inc, Waltham, Mass), presenting as grams per square centimeter, T score, and Z score. T score is the number of SDs from the mean sex-appropriate peak bone mass; Z score is the number of SDs from the mean sex- and age-appropriate bone mass. T scores for normal, mild osteopenia, severe osteopenia, and osteoporosis were –1.0 or greater, less than –1.0, less than –2.0, and less than –2.5, respectively, and were cited from a previous study.[8] The machine showed a coefficient of variation of 0.36% at L1-L4. The weight of parathyroid glands was measured during surgery using an electronic balance (model TL-300; Tanaka Scale Works Co, Tokyo, Japan). Vitamin D_3 and calcium carbonate were given routinely for at least 3 months after surgery to maintain serum levels of calcium within the reference range. Before surgery, patients with T scores less than –2.5 SDs at L1-L4 or the FN were defined as the osteoporotic group and those not meeting this condition were classified as the nonosteoporotic group.

Statistical significance was assessed using the *t* test and repeated-measures analysis of variance for unpaired and paired samples and the Wilcoxon signed rank test and χ^2 test for nonparametric data. Statistical tests were performed using the Statistical Product and Service Solutions (SPSS Inc, Chicago, Ill). $P<.05$ was considered significant. All data are presented as mean ± SD.

Table 1. Comparison of Clinical Manifestations in 20 Patients With Osteoporosis and 25 Without Osteoporosis Undergoing Parathyroidectomy for Secondary Hyperparathyroidism*

Clinical Manifestation	Patients, No. (%)		
	Osteoporotic Group	Nonosteoporotic Group	*P*
Bone pain	11 (55)	19 (76)	.20
Pruritus	11 (55)	19 (76)	.20
General weakness	7 (35)	10 (40)	.77
Diabetes mellitus	2 (10)	0	. . .
Fracture	2 (10)	0	. . .
Soft tissue calcification	0	1 (4)	. . .
Insomnia	0	1 (4)	. . .
Skin ulcer	1 (5)	0	. . .
Edema	0	1 (4)	. . .
Heart failure	0	1 (4)	. . .
Chest tightness	1 (5)	0	. . .
Failure to thrive	1 (5)	0	. . .
Hypertension	1 (5)	0	. . .

*Using the χ^2 test.

Table 2. Age, Sex, and Duration of Dialysis in 45 Patients Undergoing Parathyroidectomy for Secondary Hyperparathyroidism

Characteristic	Osteoporotic Group (n = 20)	Nonosteoporotic Group (n = 25)	*P*
Age, mean ± SD, y	50.2 ± 14.0	42.7 ± 9.1	.04*
Duration of dialysis, mean ± SD, mo	68.6 ± 36.4	73.2 ± 36.8	.68*
Sex, No.			
M	5	8	.74†
F	15	17	. . .
Hemodialysis	17	22	>.99†
Weight of parathyroid gland, mean ± SD, g	4.1 ± 2.4	3.7 ± 2.0	.60*
Identified glands, No.			
3	2	3	.64†
4	18	21	
5	0	1	

*Using the *t* test.
†Using the χ^2 test.

tween the 2 groups (**Table 1**). However, bone fractures were found in only 2 women with osteoporosis (in the FN in one women and in the ulna and radius in the other). The age of the osteoporotic group was significantly higher (50.2±14.0 years) than that of the nonosteoporotic group (42.7±9.1 years) ($P=.04$) (**Table 2**). The duration of dialysis was not significantly different between the 2 groups (Table 2). There was no significant difference between men and women with osteoporosis (Table 2). Seventeen patients in the osteoporotic group and 22 in the nonosteoporotic group were undergoing hemodialysis and the others were undergoing peritoneal dialysis. There was no significant difference between the 2 groups regarding the 2 types of dialysis (Table 2). Three to 5 glands were identified during surgery, and there was no significant difference between the 2 groups. The weight of removed glands was similar between groups (Table 2).

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Table 3. Comparison of Preoperative Laboratory Findings Between 20 Patients With Osteoporosis and 25 Without Osteoporosis Undergoing Parathyroidectomy for Secondary Hyperparathyroidism*

Serum Level†	Osteoporotic Group	Nonosteoporotic Group	*P*
Calcium, mg/dL‡ (8.00-10.00)	10.88 ± 1.00	10.80 ± 1.00	.91
Phosphorus, mg/dL§ (2.5-4.6)	6.0 ± 1.7	6.4 ± 1.5	.39
Alkaline phosphatase, U/L (24-95)	286 ± 229	284 ± 210	.21
iPTH, pg/mL‖ (10-65)	1160 ± 420	1317 ± 399	.96

*Data are given as mean ± SD. iPTH indicates intact parathyroid hormone.
†Reference ranges are given in parentheses.
‡To convert calcium from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.25.
§To convert phosphorus from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.323.
‖To convert iPTH from picograms per milliliter to picomoles per liter, multiply picograms per milliliter by 0.1053.

Table 4. Serum Levels of Calcium, Phosphorus, Alkaline Phosphatase, and iPTH 1 Day, 1 Week, and 3 Months After Surgery for Symptomatic Secondary Hyperparathyroidism*

Serum Level†	1 d (n = 45)	1 wk (n = 45)	3 mo (n = 45)
Calcium, mg/dL‡ (8.00-10.00)	8.40 ± 1.60	8.08 ± 1.48	8.88 ± 1.00
Phosphorus, mg/dL§ (2.5-4.6)	5.6 ± 2.4	3.9 ± 1.6	3.8 ± 1.4
Alkaline phosphatase, U/L (24-95)	264 ± 198	454 ± 338	153 ± 112
iPTH, pg/mL‖ (10-65)	42 ± 80	33 ± 76	90 ± 146

*Data are given as mean ± SD. iPTH indicates intact parathyroid hormone.
†Reference ranges are given in parentheses.
‡To convert calcium from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.25.
§To convert phosphorus from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.323.
‖To convert iPTH from picograms per milliliter to picomoles per liter, multiply picograms per milliliter by 0.1053.

Table 5. Comparison of Bone Mineral Density at L1-L4 and the Femoral Neck in 20 Patients With Osteoporosis and 25 Without Osteoporosis Undergoing Parathyroidectomy for Secondary Hyperparathyroidism*

Bone Mineral Density, g/cm²	Osteoporotic Group	Nonosteoporotic Group
L1-L4	0.823 ± 0.162	1.073 ± 0.187
T score	−2.868 ± 1.090	−0.6964 ± 1.224
Z score	−1.935 ± 1.140	−0.285 ± 1.263
Femoral neck	0.606 ± 0.057	0.832 ± 0.134
T score	−3.190 ± 0.918	−0.894 ± 1.181
Z score	−2.072 ± 0.926	−0.410 ± 1.296

*Data are given as mean ± SD. Using the *t* test, the T score is the SD from the mean sex-appropriate peak bone mass. The Z score is the SD from the mean age- and sex-appropriate bone mass. $P<.001$ for all.

Table 6. Comparison of Bone Mineral Density Before Surgery and 6 Months After Surgery*

Bone Mineral Density, g/cm²	Before Surgery	6 mo After Surgery
Osteoporosis (n = 20)		
L1-L4	0.823 ± 0.162†	0.915 ± 0.177†
T score	−2.868 ± 1.091‡	−2.073 ± 1.241‡
Z score	−1.935 ± 1.140	−1.167 ± 1.078
Femoral neck	0.606 ± 0.057§	0.691 ± 0.117§
T score	−3.219 ± 0.917‖	−2.345 ± 1.172‖
Z score	−2.072 ± 0.925	−1.209 ± 1.142
Nonosteoporosis (n = 25)		
L1-L4	1.084 ± 0.182†	1.162 ± 0.180†
T score	−0.653 ± 1.231‡	−0.048 ± 1.25‡
Z score	−0.303 ± 1.287	0.336 ± 1.194
Femoral neck	0.832 ± 0.134§	0.911 ± 0.132§
T score	−0.894 ± 1.181‖	−0.058 ± 1.120‖
Z score	−0.410 ± 1.296	0.402 ± 1.260

*Data are given as mean ± SD. Using the paired *t* test, $P<.001$ for all; and using repeated-measures analysis of variance, $P<.001$ for comparisons represented by †, ‡, §, and ‖ symbols.

Serum levels of calcium, phosphorus, alkaline phosphatase, and iPTH were not significantly different between the osteoporotic and nonosteoporotic groups (**Table 3**). Serum levels of iPTH had a strong correlation with weight of the parathyroid gland ($r=0.425$, $P=.004$); however, the BMD of L1-L4 and the FN had no correlation with serum levels of iPTH. Serum levels of calcium and iPTH decreased rapidly 1 day and 1 week after total parathyroidectomy and autotransplantation and gradually increased 3 months later (**Table 4**). Calcium carbonate (4-10 g) and vitamin D_3 (0.25-0.75 µg) were given for 3 months after surgery. After that time, no patient had to take calcium carbonate and vitamin D_3 regularly to keep their serum levels of calcium within the reference range. Serum levels of phosphorus decreased 1 week after surgery and remained low 3 months later. Serum levels of alkaline phosphatase increased 1 week after surgery and gradually decreased 3 months later (Table 4). One week after surgery, 4 patients had levels of iPTH above the reference range (>65 pg/mL [6.83 pmol/L]). Three months after surgery, 32 (71%) of 45 patients had levels of alkaline phosphatase above the reference range (>95 U/L) and 14 (31%) of 45 had levels of iPTH below the reference range (<10 pg/mL [1.05 pmol/L]), but none in this study had reimplantation of parathyroid tissue or kidney transplantation later. The BMDs at L1-L4 and the FN in the osteoporotic group were significantly lower than those in the nonosteoporotic groups ($P<.001$) (**Table 5**). Six months after parathyroidectomy, both groups showed an incremental increase in BMD, T scores, and Z scores. The increments at L1-L4 and the FN were 11.1% (to 0.915 g/cm² from 0.823 g/cm²) and 14% (to 0.690 g/cm² from 0.606 g/cm²), respectively, in the osteoporotic group and 7.1% (to 1.162 g/cm² from 1.084 g/cm²) and 9.4% (to 0.911 g/cm² from 0.832 g/cm²), respectively, in the nonosteoporotic group. Patients with osteoporosis had better recovery than those without osteoporosis ($P<.001$) (**Table 6**). Recovery of osteopenia or osteoporosis was also found 6 months after parathyroidectomy at L1-L4 and the FN ($P<.001$ for both) (**Table 7**).

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COMMENT

Bone pain, pruritus, general weakness, and soft tissue calcification are well-known manifestations of elevated PTH levels in patients with secondary hyperparathyroidism. However, only a few systemic studies[9,10] have been reported about the recovery of BMD or osteoporosis after surgery for secondary hyperparathyroidism. Recently, in a large series[11,12] of nonselected patients undergoing dialysis, adynamic bone disease emerged as the most common bone disease in patients with end-stage renal failure. In the early studies, adynamic bone disease was associated with aluminum overload,[13] but more recently it has been shown that the same histological lesion could be found without aluminum.[14-17] Adynamic bone disease could also cause osteopenia and theoretically was dramatically worsened by parathyroidectomy. Levels of iPTH enabled discrimination between adynamic bone disease and osteitis fibrosa. Intact PTH concentration emerged as the most helpful investigation, with adynamic bone disease being found with normal levels and osteitis fibrosa found with elevated levels (>199 pg/mL [21 pmol/L]).[18] In symptomatic patients in whom iPTH levels were in the nondiagnostic range, or in cases where aluminum overload was suspected, bone biopsy remained the gold standard.[17] In this study, patients with symptomatic secondary hyperparathyroidism who underwent surgery all had levels of iPTH greater than 649 pg/mL (68.3 pmol/L), normal levels of aluminum, and no response to vitamin D_3 treatment; thus, we did not perform bone biopsy. The chance of adynamic bone disease and the worse BMD after parathyroidectomy had never been found. The clinical manifestations were similar between the 2 groups, except that bone fractures were found only in the osteoporotic group. The BMD was often reduced in patients with primary hyperparathyroidism and was usually reversible after parathyroidectomy.[8,9,19-21] In experimental rats with secondary hyperparathyroidism, high levels of PTH (>52.6 ng/L [500 pg/mL]) resulted in substantial cortical bone loss but cancellous bone gain.[22] In this study, there was no significant difference between bone loss at L1-L4 and the FN. This differs from a previous study,[23] in which patients receiving chronic dialysis had loss of BMD that was much more pronounced in the FN than in the lumbar spine. Our research leads us to believe that bone loss in patients with symptomatic secondary hyperparathyroidism was marked at both L1-L4 and the FN, and the differences between the 2 sites were not significant.

There have been few studies measuring BMD at multiple sites after parathyroidectomy for secondary hyperparathyroidism. After successful parathyroidectomy, the bone mass of the distal radius and lumbar spine increased approximately 10% within 3 months and then remained stable during the first year after surgery.[9] In the present research, we observed similar findings and also found that patients with osteoporosis had better recovery than those without osteoporosis. The age of the osteoporotic group was higher than that of the nonosteoporotic group, and this result matched that reported previously.[24,25] It has been reported[26] that the duration of dialysis has no relationship to osteoporosis, which agrees with our findings. Diabetes mellitus has been claimed to predispose patients to adynamic bone disease but has never been reported to relate to osteitis fibrosa.[25] In the present study, 2 of 20 patients in the osteoporotic group had diabetes mellitus. Because of so few cases with diabetes mellitus, no conclusion was made. In this study, we found that serum levels of calcium, phosphorus, alkaline phosphatase, and iPTH were similar between the osteoporotic and nonosteoporotic groups. Also, the BMD of L1-L4 and the FN had no relation to the levels of iPTH in this and a previous study.[3] The changes in serum levels of calcium, phosphorus, alkaline phosphatase, and iPTH after parathyroidectomy and autotransplantation were similar to our previous findings.[6] One week after surgery, 4 patients had iPTH levels above the reference range, perhaps caused by supernumerary or missing glands. Because their levels of iPTH were less than one quarter of their original levels and their levels of calcium and their symptoms improved, no further studies were done on these 4 patients. Although 3 months after parathyroidectomy 71% (32/45) of the patients had alkaline phosphatase levels above the reference range and 31% (14/45) had levels of iPTH below the reference range, the recovery of BMD and osteoporosis was still good. Because so few patients were undergoing peritoneal dialysis in this study, we did not find any significant difference in BMD at L1-L4 and the FN between patients undergoing continuous ambulatory peritoneal dialysis vs regular hemodialysis as reported earlier.[27] Six months after surgery, changes in BMD, T scores, and Z scores were found in the osteoporotic and nonosteoporotic groups. However, recovery in the osteoporotic group was better than that in the nonosteoporotic group ($P<.001$) (Table 5). This is a new finding that we believe has never been reported before. Osteopenia or osteoporosis at L1-L4 and the FN found in patients with symptomatic secondary hyperparathyroidism and high levels of iPTH could be improved after parathyroidectomy and autotransplantation. The osteoporosis found in secondary hyperparathyroidism had no specific clinical manifestations ex-

Table 7. Recovery of Osteopenia or Osteoporosis in L1-L4 and the Femoral Neck 6 Months After Parathyroidectomy in 45 Patients With Symptomatic Secondary Hyperparathyroidism*

	Patients, No.		
	Before Surgery	6 mo After Surgery	*P*
L1-L4			
Normal	14	20	
Mild osteopenia	10	13	
Severe osteopenia	6	4	
Osteoporosis	15	8	<.001
Femoral neck			
Normal	11	23	
Mild osteopenia	11	9	
Severe osteopenia	6	3	
Osteoporosis	17	10	<.001

*Using the Wilcoxon signed rank test. Normal indicates a T score ≥−1.0; mild osteopenia, −1.0<T score ≥−2.0; severe osteopenia, −2.5≤T score <−2.0; and osteoporosis, T score <−2.5.

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cept for bone fracture and older age. We recommend that BMD be checked routinely in every patient undergoing regular dialysis. If high levels of iPTH (>649 pg/mL [68.3 pmol/L]) cannot be suppressed by administering vitamin D_3, patients who have symptomatic secondary hyperparathyroidism and osteoporosis should have parathyroidectomy early to prevent the morbidity of bone fracture. We also found that parathyroidectomy and autotransplantation can improve BMD of symptomatic secondary hyperparathyroidism at L1-L4 and the FN.

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Quotation

I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work.

Harvey Cushing
1869-1939

Reference: Letter to Dr Henry Christian, November 20, 1911.

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