Calcimimetics Versus Parathyroidectomy for Treatment of Primary Hyperparathyroidism

Retrospective Chart Analysis of a Prospective Database

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Objective: This study aims to determine the efficacy of calcimimetics in improving bone mineral density (BMD) in patients with primary hyperparathyroidism (pHPT) and compare those results to patients undergoing parathyroidectomy.

Background: Parathyroidectomy has been shown to improve BMD in pHPT, but calcimimetics have recently been advocated as a medical alternative to parathyroidectomy for pHPT.

Materials and Methods: We identified 17 patients that were treated with calcimimetics for pHPT. Seventeen patients with pHPT who underwent parathyroidectomy served as surgical controls. Serum calcium level, parathyroid hormone (PTH) level, and femur and spine BMD T scores were compared before and 1 year after therapy.

Results: Both groups were demographically matched. Calcium levels normalized in 70.6% of medically versus 100% of surgically treated patients ($P = 0.026$). PTH levels normalized in 35% of patients treated with calcimimetics versus 76% of surgical patients ($P = 0.036$). Femur BMD improved in 18.8% of medically treated patients versus 58.8% of surgical patients ($P = 0.032$). Spine BMD improved in 70.6% of medically treated patients versus 82.4% of surgical patients ($P = 0.69$). Further analysis demonstrated that regardless of treatment, normalization of PTH was associated with significant improvement in femur ($P = 0.03$) and spine BMD ($P < 0.001$). Normalization of calcium without normalization of PTH did not impact BMD.

Conclusions: Parathyroidectomy results in greater normalization of serum calcium and PTH levels and significantly improves cortical BMD compared to calcimimetics. Regardless of treatment, normalization of PTH is associated with significant improvement in spine and femur BMD, suggesting that the superior effects of surgery may be mediated by better control of PTH.

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Primary hyperparathyroidism (pHPT) is a common endocrine disease with a prevalence of 1 to 4 per 1000 inhabitants and a female to male ratio of 3:1 in the United States.[1] It is the consequence of a single autonomous adenoma of the parathyroid gland in 85% to 90% of cases and is characterized by hypercalcemia and an unsuppressed parathyroid hormone (PTH) concentration. Classic symptoms of pHPT include nephrolithiasis, neuromuscular weakness, fatigability, impaired cognitive function, and loss of bone mineral density (BMD). Parathyroidectomy is recognized as the gold standard for symptomatic patients and for "asymptomatic" patients meeting either one of the following NIH Consensus Development Conference criteria: (1) a serum calcium concentration of more than 1.0 mg/dL above upper limit of normal, (2) a 24-hour urine calcium excretion of more than 400 mg per 24 hour, (3) a creatinine clearance more than 30% below normal, (4) age less than 50 years, or (5) a bone density T score less than −2.5 SD at any site.[2]

Several studies have previously demonstrated that parathyroidectomy induces a normalization of serum calcium levels, a decrease of PTH levels, and regain of BMD.[3–7] The greatest reduction in BMD in patients with pHPT is classically found at the site of cortical bone, that is, the radius and the femur, whereas cancellous bone, such as the spine, are usually less affected.[7] This is thought to be due to a higher vulnerability of cortical bone to the catabolic effects of PTH.[8]

Some patients with pHPT do not seek surgical intervention, because they view the potential complications related to the procedure or the anesthesia as too great relative to the expected benefits. Current medical therapy for secondary hyperparathyroidism includes bisphosphonates and more recently, calcimimetics.

Calcimimetic agents act on the calcium-sensing receptors on parathyroid cells and allosterically modulate it, thereby enhancing its sensitivity to circulating calcium concentrations and decreasing PTH secretion.[9–11] They have been effective at controlling serum calcium levels in patients with pHPT,[3,12–14] but are currently indicated and FDA approved only in the setting of secondary hyperparathyroidism in patients with end-stage renal disease.[15] It remains unclear if they can achieve similar effects to parathyroidectomy in patients with pHPT and therefore provide a select group of patients with a valuable alternative to surgery.

In this study, we aimed to determine the efficacy of calcimimetics in improving femur and spine BMD in patients with pHPT compared to those undergoing parathyroidectomy. As an additional end point, we studied the changes in calcium and PTH levels when comparing these 2 groups.

MATERIALS AND METHODS

Patient Selection, Study Design, and Follow-Up

This study is a retrospective review of a prospective database at a tertiary referral center. Institutional review board approval from the New York Presbyterian Hospital–Weill Cornell Medical Center was obtained. A total of 475 patient charts with pHPT treated in the divisions of endocrine surgery and endocrinology at our institution between 2000 and 2007 were reviewed. Patients were included in this study if they had a confirmed biochemical (elevated serum PTH and serum calcium levels) and radiological (CT, technetium Tc 99m sestamibi scan, and/or ultrasound of the neck) diagnosis of pHPT apparently due to a single-gland parathyroid adenoma. All patients within the parathyroidectomy group and 15 of 17 patients within the calcimimetic group had 2 concordant localization studies. Two patients within the calcimimetic group had a sestamibi scan only.

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Pre- and posttreatment BMD T scores of femur and spine as well as PTH- and calcium serum levels were obtained pretreatment and at least 1 year after treatment for all study subjects in both groups. All surgical specimens were examined by an endocrine surgical pathologist. Patients with a diagnosis of parathyroid carcinoma, concurrent renal disease, or hyperparathyroidism due to causes other than stated in the inclusion criteria were excluded from this study. Moreover, patients who underwent surgical intervention and had inappropriate normalization of intraoperative PTH or greater than 1 single-gland adenoma were also excluded. All patients treated medically qualified for surgical intervention but deferred for medical treatment. All medical and surgical patients had correction of deficient vitamin D levels as part of their treatment.

Treatment

Surgical treatment consisted of resection under local anesthesia with sedation. All surgical patients met accepted criteria for adequate surgical treatment on the basis of the intraoperative PTH assay. Specifically, a more than 50% drop of the preexcision PTH level and decline into the normal range at least 10 minutes after the adenoma was removed was used for assessment of adequate surgical therapy. All surgically treated patients had serum calcium and PTH levels measured postoperatively within 2 weeks, then at 6 months and yearly thereafter.

Patients treated medically were followed by an endocrinologist and treated with a calcimimetic in combination with bisphosphonates (Fosamax, Actonel, Zometa, or Aredia), except for 1 patient who received calcimimetics alone. The dose of calcimimetics was determined by the treating endocrinologist based on extensive experience treating patients with secondary hyperparathyroidism. The starting dose (Sensipar, Amgen Inc) was 30 or 60 mg daily, except for 1 patient who received a daily starting dose of 15 mg. Serum calcium, phosphorus, and PTH levels were measured within 1 week after initiation of therapy and the dose was then titrated to optimize calcium and PTH levels. Once a maintenance dose was established, serum calcium and phosphorus were monitored monthly, and serum PTH levels quarterly.

Normal serum calcium and PTH levels were defined on the basis of our laboratory criteria as ranging from 8.5 to 10.4 mg/dL and from 10 to 68 pg/mL, respectively. Osteopenia and osteoporosis were defined as a BMD T score between −1 and −2.5 SD and more than −2.5 SD respectively, according to the World Health Organization standards.

Statistical Analysis

Continuous variables were compared using a 2-tailed *t* tests. Paired samples were also analyzed using paired *t* tests. Categorical variables were analyzed using the Fisher exact test. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using the *R* statistical software (Version 2.10.1, http://www.r-project.org/).

RESULTS

Seventeen patients treated with calcimimetics for pHPT who met inclusion criteria were identified and matched with 17 patients with pHPT who underwent parathyroidectomy. All patients in the calcimimetic group were females. The surgery group comprised 1 man and 16 women. The mean age difference between these 2 groups was not statistically significant—71.9 years for the calcimimetic and 67.4 years for the parathyroidectomy group ($P = 0.062$). Mean follow-up time was similar between both groups, 775 days in the calcimimetic group versus 639 days in the parathyroidectomy group ($P = 0.336$) (Table 1). All patients in the calcimimetic group were treated medically for at least 1 year. There were no complications in the surgery group (ie, bleeding, infection, or laryngeal nerve injury) or side effects due to medical treatment in the calcimimetic group. The operative failure rate was 0%, because all patients within the parathyroidectomy group were normocalcemic at 1 year after surgery.

Treatment efficacy was assessed by comparing pre- and posttreatment serum calcium and PTH levels as well as spine and femur BMD T scores. Mean pretreatment serum calcium levels were 10.79 mg/dL and 10.77 mg/dL in the calcimimetic and surgery groups, respectively ($P = 0.95$). Mean posttreatment serum calcium levels in the calcimimetic group were 10.14 mg/dL versus 9.48 mg/dL in the surgery group ($P = 0.002$) (Table 2). Serum calcium values were significantly different when comparing pre- and posttreatment values within the calcimimetic group ($P = 0.003$) and within the surgery group ($P < 0.001$) (Table 3). Normalization of calcium levels occurred in 70.6% (12/17) of medically treated patients and in 100% (17/17) of surgically treated patients ($P = 0.026$).

Mean pretreatment serum PTH levels were 115.8 pg/mL and 183.2 pg/mL in the calcimimetic and surgery groups, respectively ($P = 0.086$). Mean posttreatment serum PTH levels in the calcimimetic group were 92.8 pg/mL versus 55 pg/mL in the surgery group ($P = 0.04$) (Table 2). Serum PTH values were not significantly different when comparing pre- and posttreatment values within the calcimimetic group ($P = 0.082$) but were significantly different within the surgery group ($P = 0.001$) (Table 3). Serum PTH levels normalized in 35% (6/17) of patients treated with calcimimetics versus 76% (14/17) of patients undergoing parathyroidectomy ($P = 0.036$).

BMD measurements showed that 47% (8/17) of patients within the calcimimetic group had osteopenia versus 64.7% (11/17) of patients in the parathyroidectomy group ($P = 0.49$); 47% (8/17) of patients in the calcimimetic group had osteoporosis versus 35.3% (6/17) in the surgery group ($P = 0.73$).

The mean pretreatment femur BMD T score was −2.25 in the calcimimetic and −1.82 in the surgery group ($P = 0.17$). Mean posttreatment femur BMD T score in the calcimimetic group was −2.4 versus −1.69 in the surgery group ($P = 0.033$) (Table 4).

TABLE 1. Patients Demographics and Average Follow-Up Time

	Calcimimetics	Surgery	*P*
No. patients	17	17	
Age (yrs)*	71.9 ± 8.5	67.4 ± 6.67	0.062
Sex			0.39
Male	0	1	
Female	17	16	
Follow-up (d)*	775 ± 512	639 ± 257	0.34

*Mean ± SD.

TABLE 2. Pre- and Posttreatment Serum Calcium and PTH Levels: Calcimimetics Versus Parathyroidectomy

	Calcimimetics	Surgery	*P*
Calcium (mg/dL)*†			
Pretreatment	10.79 ± 0.63	10.77 ± 0.44	0.95
Posttreatment	10.14 ± 0.69	9.48 ± 0.35	0.002
PTH (pg/mL)*‡			
Pretreatment	115.8 ± 85	183.2 ± 131	0.086
Posttreatment	92.8 ± 67	55 ± 25	0.04

*Mean ± SD.
†Normal calcium level: 8.5–10.4 mg/dL.
‡Normal PTH level: 10–68 pg/mL.

TABLE 3. Pre- and Posttreatment Values Within the Calcimimetic and Surgery Groups, Respectively

	Calcimimetics			Surgery		
Parameters	**Pretreatment**	**Posttreatment**	***P***	**Pretreatment**	**Posttreatment**	***P***
Calcium (mg/dL)*	10.79	10.14	0.003	10.77	9.48	<0.001
PTH (pg/mL)†	115.8	92.8	0.082	183.2	55	0.001
Femur T score‡	− 2.25	− 2.4	NI§	− 1.82	− 1.69	0.19
Spine T score‡	− 1.9	− 1.45	0.045	− 1.94	− 1.6	0.017

*Normal Calcium Level: 8.5–10.4 mg/dL.
†Normal PTH Level 10–68 pg/mL.
‡Osteopenia: −1.5 to −2.5, Osteoporosis: >−2.5.
§NI: No improvement in BMD T score.

TABLE 4. Pre- and Posttreatment Mean Femur and Spine BMD T Scores: Calcimimetics Versus Parathyroidectomy

	Calcimimetics	Surgery	***P***
Femur T score*†			
Pretreatment	−2.25 ± 0.8	−1.82 ± 1.0	0.17
Posttreatment	−2.4 ± 0.6	−1.69 ± 1.1	**0.033**
Spine T score*†			
Pretreatment	−1.9 ± 1.2	−1.94 ± 1.1	0.92
Posttreatment	−1.45 ± 1.4	−1.6 ± 1.3	0.75

*Mean ± SD.
†Osteopenia: −1.5 to −2.5, Osteoporosis: >−2.5.

Although femur BMD T scores were improved when comparing pre- and posttreatment values within the surgery group, the improvement was not statistically significant ($P = 0.19$). Femur BMD T scores worsened in the calcimimetic group, although not at a statistically significant level either ($P = 0.29$) (Table 3). Improvement in femur BMD T scores was noted in only 18.8% (3/16) of medically treated patients versus 58.8% (10/17) of patients undergoing parathyroidectomy ($P = 0.032$).

The mean pretreatment spine BMD T score was −1.90 in the calcimimetic and −1.94 in the surgery group ($P = 0.92$). Mean posttreatment spine BMD T score in the calcimimetic group was −1.45 versus −1.6 in the surgery group ($P = 0.75$) (Table 4). Spine BMD T scores were significantly improved when comparing pre- and posttreatment values within the calcimimetic group ($P = 0.045$), and within the surgery group ($P = 0.017$) (Table 3). Improvement in spine BMD T scores was noted in 70.6% (12/17) of medically treated patients versus 82.4% (14/17) of patients undergoing parathyroidectomy ($P = 0.69$).

Subgroup analysis aimed to compare femur and spine BMD T scores with (1) normalization of PTH only, (2) normalization of calcium only, (3) normalization of PTH plus calcium levels, and (4) normalization calcium levels without normalization of PTH (Table 5). When serum PTH levels normalized posttreatment, femur BMD T scores improved by 11% ($P = 0.028$) and spine BMD T scores improved by 22% ($P < 0.001$). When serum PTH levels did not normalize posttreatment, femur ($P = 0.10$) and spine BMD T scores ($P = 0.18$) were not significantly affected. In patients with normalization of serum calcium levels there was a significant improvement of spine BMD T scores with an overall increase of 22% ($P = 0.002$). However, femur BMD T scores only improved by 4% ($P = 0.22$). In the group without normalization in serum calcium levels, there was also no significant improvement in the mean femur and spine BMD T score ($P = 0.26$ and $P = 0.66$). In patients with normalization of both serum PTH and calcium levels, there was improvement of 11% for the femur ($P = 0.022$) and 22% for the spine BMD T score ($P < 0.001$) posttreatment. There was no significant improvement of the femur or spine BMD T score in the patient group without normalization of either PTH or calcium levels. Finally, when calcium levels but not PTH levels normalized, femur BMD T scores decrease by 5% ($P = 0.19$) and although spine BMD T scores did improve by 23% it was not significant ($P = 0.18$).

DISCUSSION

In this study, we aimed to compare outcomes of calcimimetic-based medical therapy versus surgical treatment in patients with pHPT due to single adenoma. Calcimimetics could become a popular alternative to parathyroidectomy, in addition to bisphosphonates, in patients with pHPT, if they can achieve similar end results as parathyroidectomy and avoid the possible complications of surgical intervention. We analyzed 3 specific objective end points (normalization of serum calcium, decrease of serum PTH levels, and improvement of BMD T scores) in patients with pHPT to determine the efficacy of calcimimetic agents when compared to surgery.

Normalization of serum calcium levels was achieved in 70.6% of patients treated with calcimimetics compared to 100% of patients treated by surgical resection. These findings are similar to previous reports for normalization of calcium levels in pHPT patients treated with calcimimetics.[12–14] Peacock et al reported normalization of calcium levels in 74% to 100% of patients after 15 days, 1 year, and 5 years of daily intake of calcimimetic agents in pHPT patients.

Serum PTH levels normalized in 35% of patients treated medically and 76% of patients treated surgically. Four patients failed to normalize serum PTH after surgical intervention. Previous reports have demonstrated that within 1 week to 5 years after parathyroidectomy, 9% to 62% of patients with surgically treated pHPT and a normal postoperative serum calcium level are found to have elevated serum PTH levels. Underlying mechanisms for normocalcemic persistent elevation in postoperative PTH remain unclear.[3] However, an elevated postoperative PTH concentration was not found to be predictive of surgical failure as measured by recurrent hypercalcemia.[16] Previous studies have indicated that serum PTH levels uncommonly normalize in patients treated with calcimimetic agents, and when PTH levels do normalize, it appears to be a transient effect.[12,13] Patients treated with calcimimetics in this study showed a similar pattern of PTH normalization, with less than half of patients in that group having posttreatment serum PTH levels improving into the normal range.

Femur BMD T scores were significantly improved and almost within normal range after parathyroidectomy when comparing pre- and posttreatment values. Several previous studies have confirmed these findings,[5–7] which match the general consensus that bone

TABLE 5. Pre- and Posttreatment Mean Femur and Spine BMD T Scores After Normalization of PTH Calcium and PTH + Calcium Serum Levels in Patients Treated Either Medically or Surgically

	Normalization of PTH (n = 15)			No Normalization of PTH (n = 20)		
Parameters	**Pretreatment**	**Posttreatment**	***P***	**Pretreatment**	**Posttreatment**	***P***
Femur T score	− 1.9	1.71	0.028	− 2.15	− 2.38	NI*
Spine T score	− 2.17	− 1.69	<0.001	− 1.67	− 1.35	0.18
	Normalization of Calcium (n = 30)			**No Normalization of Calcium (n = 5)**		
Parameters	**Pretreatment**	**Posttreatment**	***P***	**Pretreatment**	**Posttreatment**	***P***
Femur T score	− 2.07	− 1.98	0.22	− 1.8	− 2.3	NI*
Spine T score	− 2.03	− 1.58	0.002	− 1.28	− 1.18	0.66
	Normalization of PTH + Calcium (n = 14)			**No Normalization of PTH + Calcium (n = 21)**		
Parameters	**Pretreatment**	**Posttreatment**	***P***	**Pretreatment**	**Posttreatment**	***P***
Femur T score	− 1.9	1.69	0.022	− 1.78	− 2.38	NI*
Spine T score	− 2.2	− 1.75	<0.001	− 1.3	− 1.27	0.86
	Normalization of Calcium Without PTH (n = 16)					
Parameters	**Pretreatment**	**Posttreatment**	***P***			
Femur T score	− 2.28	− 2.38	NI*			
Spine T score	− 1.77	− 1.38	0.18			

*NI = No improvement in BMD T score.

density improves significantly in cortical bone sites after parathyroidectomy in patients with pHPT. In contrast, calcimimetic treatment did not significantly improve femur BMD T scores in this study, which is also consistent with previous reports.[12,13,17]

Parathyroidectomy also significantly improved spine BMD T scores in our patient population, which is consistent with previous reports.[4–6] Surprisingly, the calcimimetic group also had significant improvement of spine BMD T scores, which is contrary to prior studies that showed no improvement in spine BMD T scores for patients treated with calcimimetics alone with primary or secondary hyperparathyroidism.[13,18,19] This may be due to the combined effect of calcimimetics plus bisphosphonate therapy on the spine BMD. Bisphosphonates have been shown to work on a tissue level through inhibition of bone destruction and increase in BMD by decrease of bone resorption and bone turnover.[20] Indeed, previous studies have shown that bisphosphonates cause a greater improvement in spine BMD when compared to the femur BMD.[20–22]

Subgroup analysis demonstrated that regardless of treatment, normalization of serum PTH levels yields significant improvements in both femur and spine BMD T scores. However, when calcium levels normalized without normalization of PTH levels, neither femur nor spine BMD improved significantly. This observation suggests that calcium may be a confounder in BMD improvement and that the superior effects of surgery over calcimimetic treatment may ultimately be mediated by better control of PTH.

In this study we did not observe any complications in either the surgical or the medical group. Side effects due to calcimimetic treatment have been documented to include nausea, vomiting, and diarrhea in 5% or more cases.[23] It is likely that side effects of calcimimetics were not seen in this study population because of the fact that patients were selected for inclusion only if they had been maintained on a calcimimetic agent for at least 1 year.

There were 3 major limitations to our study. The first is the retrospective nature of the analysis, which leads to differences in treatment, specifically the failure to follow a protocol for dose escalation of calcimimetic agents. The second limitation is the diagnosis of single parathyroid adenoma based on imaging in the calcimimetic group. None of these patients underwent surgery for definitive diagnosis. However, the majority of these patients had at least 2 imaging studies, which were concordant, to localize the adenoma. Most studies have shown localization with 2 concordant studies is 96% accurate for single adenoma detection.[24] The third major limitation is the study size. Although the study was powered to answer specific questions, larger studies would be beneficial for subgroup analysis. At our center very few patients elect for medical management in pHPT making recruitment in this arm difficult. Most prior studies analyzing the effectiveness of calcimimetic agents also included small group sizes, probably for similar reasons.[12–14] Prospective multicenter randomized trials may be more effective in eliminating these limitations. Despite these limitations our study shows that calcimimetic agents do not achieve similar results than parathyroidectomy in patients with pHPT when comparing serum calcium and PTH levels as well as femur and spine BMD T scores.

In conclusion, parathyroidectomy results in greater normalization of serum calcium and PTH levels and significantly improves cortical BMD compared to calcimimetics. Regardless of treatment, normalization of PTH is associated with significant improvement in spine and femur BMD, suggesting that the superior effects of surgery may be mediated by better control of PTH. Larger, prospective trials are needed to confirm these results and define the utilization of calcimimetic agents in the setting of pHPT.

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