Bisphosphonates can reduce bone hunger after parathyroidectomy in patients with primary hyperparathyroidism and osteitis fibrosa cystica

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ABSTRACT

Objective: To assess the effect of bisphosphonates on post-parathyroidectomy hypocalcemia in patients with osteitis fibrosa cystica. **Methods:** Review of the medical records of six patients using bisphosphonates preoperatively. **Results:** Mean age was 35.6 ± 10.5 years; serum calcium = 13.51 + 0.87 mg/dL; iPTH = 1,389 + 609 pg/mL. The mean value of urine deoxypyridinoline (UDPD) of three patients was 131 ± 183 nmol/mmol Cr, and of C-telopeptide (CTX), 2,253 ± 1,587 pg/mL. The mean values of bone densitometry (T score) were as follows: 0.673 ± 0.150 g/cm^2 (-4.42 ± 1.23) in lumbar spine (L2-L4); 0.456 ± 0.149 g/cm^2 (-5.58 ± 1.79) in the femoral neck; and 0.316 ± 0.055 g/cm^2 (-5.85 ± 0.53) in radius 33. Patient 1 received oral alendronate, 30 mg/day for four weeks; his calcium decreased from 14 to 11.6 mg/dL, and his UDPD from 342 to 160 nmol/mmol Cr. Patient 2 received oral alendronate, 20 mg/day for six weeks; his calcium decreased from 14 to 11.0 mg/dL and his UDPD from 28.8 to 14 nmol/mmol Cr. Patient 3 received intravenous pamidronate, 90 mg prior to surgery. Patient 4 received oral alendronate, 140 mg/week for six weeks; her calcium decreased from 13.7 to 12.3 mg/dL and her CTX from 2,160 to 1,340 pg/mL. Patient 5 received oral alendronate, 140 mg/week for six weeks; her calcium levels dropped from 14.3 to 14.1 mg/dL; her CTX did not change. Patient 6 received ibandronate, 150 mg, ten days prior to surgery; his CTX reduced by 62%. No patient developed severe hypocalcemia in the first postoperative week. One year after surgery, the mean gain in bone mineral density was 40% ± 29% in L2-L4, 86 ± 39% in the femoral neck, and 22% ± 11% in radius 33. **Conclusion:** The preoperative use of bisphosphonates seems to attenuate bone hunger without preventing a significant increase in bone mass in the follow-up of parathyroidectomy.

Keywords: hyperparathyroidism, bone, bisphosphonates.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disorder of the mineral metabolism characterized by hypersecretion of the parathyroid hormone (PTH).[1] Approximately 80% of the patients have the asymptomatic form. Kidney stones occur in 15%-20% of the patients, and bone disease in less than 5%.[2] The diagnosis of PHPT is based on detection of hypercalcemia and high PTH levels.[3,4] Although most patients are considered asymptomatic, many can report unspecific manifestations, including musculoskeletal symptoms, such as fatigue, muscle weakness, myalgia, and fibromyalgia symptoms.[5]

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The prevalence and cause of such symptoms, however, have not yet been totally clarified. A Brazilian study has reported a reduction in those symptoms in 61.5% of 15 patients submitted to parathyroidectomy.[6] Bone pain can occur due to osteoporotic fractures or to osteitis fibrosa cystica (OFC).

Osteitis fibrosa cystica is the severe form of PHPT, in which typical radiological alterations, such as osteoclastoma, occur. The measurements of urine N-telopeptide and serum C-telopeptide are significantly increased in patients with the severe bone disease. Those bone markers usually undergo a significant reduction after parathyroidectomy.[7] Usually most patients with OFC develop severe hypocalcemia right after parathyroidectomy due to the bone hunger syndrome, which is secondary to high bone remodeling and more noticeable in the concomitant vitamin D defficiency.[4,7-9] During hyperparathyroidism, a state of intense bone remodeling exists, resulting in calcium efflux from the bone. After parathyroidectomy, the sudden drop in PTH levels causes an imbalance between bone formation by osteoblasts and osteoclast-mediated bone resorption, affecting calcium bone flow and leading to an intense increase in that ion uptake by bone, causing hypocalcemia.[10] In patients with mild PHPT, bisphosphonates reduce bone remodeling and the serum levels of calcium. Older studies have disclosed the risk of "frozen bone", that is, bisphosphonates preventing the bone mass gain occurring after parathyroidectomy. However, literature data about the preoperative use of bisphosphonates in patients undergoing parathyroidectomy are very scarce, especially in patients with OFC.

This study aimed at describing the effect of bisphosphonates on bone remodeling and on preventing severe hypocalcemia caused by bone hunger syndrome after parathyroidectomy in six patients with severe PHPT.

METHODS

This study assessed six patients diagnosed with OFC who used bisphosphonates preoperatively. All data were collected through medical record review. The study was approved by the Ethics Committee of the Hospital Agamenon Magalhães (CEP protocol: 276/2006).

The VITROS 950 system (Johnson-Johnson Company) was used to measure calcium, phosphorus (P), alkaline phosphatase, 24-hour calciuria. Electrochemiluminescence (Elecsys, Roche Diagnostics GmbH, Mannheim, Germany) was used to measure serum PTH and the following bone resorption markers: urine deoxypyridinoline (UDPD), and serum NTX (N-telopeptide) or CTX (C-telopeptide). The interassay and intra-assay coefficients of variation were 10% and 12%, respectively. The measurements of calcium and bone resorption markers were performed at the beginning and after the end of treatment with bisphosphonates in the preoperative period. Serum calcium was also measured on the first day after parathyroidectomy.

Bone densitometry was performed in all patients prior to bisphosphonate use and in four patients one year after surgery. Bone mineral density was measured in the lumbar spine (L2-L4), femoral neck, and distal forearm by use of dual-energy X-ray absorptiometry (Lunar Corporation Madison, Wisconsin, USA), and the results were expressed in g/cm^2 and T-score. The coefficient of variation was 0.9% for L2-L4, 1.2% for the femoral neck, and 2% for radius 33.

The inclusion criteria were as follows: patients diagnosed with PHPT, confirmed by hypercalcemia (serum calcium > 10.2 mg/dL) and high PTH; presence of radiological characteristics compatible with OFC, such as brown tumor (osteoclastoma), subperiostal bone resorption, and "salt and pepper" demineralization of the skull; and osteoporosis on bone densitometry.[11] The exclusion criteria were as follows: bisphosphonate use in the six months preceding the drug use in the preoperative period; hormone replacement therapy or concomitant antiresorptive therapy; use of medications that interfere with bone metabolism, such as anticonvulsants, corticosteroid, and excess of vitamin D or A; other concomitant diseases that interfere with bone metabolism, such as Paget's disease, osteogenesis imperfecta, rheumatoid arthritis, and systemic lupus erythematosus; serum creatinine > mg/dL; history of allergy or intolerance to bisphosphonates; active upper gastrointestinal symptoms.

CASE REPORTS

Case 1: The patient is a 32-year-old black male with history of fracture in the right lower limb (RLL), left clavicle, and left upper limb (LUL) four years earlier, and in the femoral neck ten months earlier. On physical examination, the patient was in regular general condition, had healthy coloring and no fever. A hard nodule was palpated on the upper lobe of his thyroid. The cardiovascular and respiratory systems were within the normal range, blood pressure (BP) was 120 × 80 mmHg, and heart rate (HR) was 80 bpm. The abdomen showed no alterations. The patient complained of pain upon movement of his lower limbs, which prevented him from walking, in addition to redness and local warmth on the right knee. The following tests were performed: iPTH = 1,196.0 pg/mL; serum calcium = 14 mg/dL; alkaline

phosphatase = 717 UI/L; osteocalcin = 234.4 ng/mL; 24-hour urine creatinine = 1,056.0 mg/24 h; UDPD = 342.8 nmol/mmol of creatinine. Bone densitometry: radius 33 = 0.303 g/cm^2 (-6.04 SD); L2-L4 = 0.517 (-5.58 SD); femoral neck = .350 g/cm^2 (-8.62 SD). Treatment with alendronate, 30 mg/day for 30 days, was initiated. New laboratory tests were performed: UDPD = 160.5 nmol/mmol of creatinine; calcium = 11.6 mg/dL. The patient underwent partial thyroidectomy + subtotal parathyroidectomy (histopathology: parathyroid adenoma). In the postoperative period, the patient had mild hypocalcemia (paresthesia and cramps), which required only oral calcium. Postoperative exams: iPTH = 5.2 pg/mL; calcium = 7.4 mg/dL. Bone densitometry: radius 33 = 0.384 g/cm^2 (-5.17 SD); L2-L4 == 0.673 g/cm^2 (-4.73 SD). One year after parathyroidectomy, the bone mass gain shown on densitometry was 26% in radius 33, and 30% in L2-L4.

Case 2: The patient is a 25-year-old white male complaining of bone pain, mainly in lower limbs and lumbar region, in addition to generalized muscle weakness for one year. Shortly after, the patient noticed a tumor in his right thigh, and underwent orthopedic surgery (histopathology compatible with aneurysmatic bone cyst). On physical examination, the patient was in regular general condition, pale (++/4+), and had no fever. A hard nodule of approximately 3.0 cm was observed on the left lobe of the thyroid. No cardiovascular and respiratory sign of abnormality (BP = 130 × 80 mmHg, HR = 80 bpm) and no abdominal alterations were seen. Two surgical scars on the thigh and medial side of the right knee, and a tumor on the lateral side of the left thigh were observed. The laboratory tests were as follows: iPTH = 746 pg/mL; calcium = 14.0 mg/dL; calciuria = 367.2 mg/24 h; alkaline phosphatase = 2,820 UI/L; UDPD = 28.8 nmol/mmol of creatinine. Bone densitometry: radius 33 = 0.409 g/cm^2 (-4.93 SD); L2-L4 = 0.779 g/cm^2 (-3.84 SD); femoral neck = 0.430 g/cm^2 (-5.33 SD). Cervical ultrasound showed a solid 3.6-cm nodule, posterior to the left lobe of the thyroid. Full-body Sestamibi scintigraphy evidenced increased uptake in the left lower parathyroid and areas of increased uptake in the left femur. Alendronate, 20 mg/day for six weeks, was started, and progressive improvement of the asthenia and a reduction in the left thigh tumor were observed. The patient underwent parathyroidectomy (histopathology compatible with parathyroid carcinoma with capsule invasion and vascular permeation). In the postoperative period, the patient had mild hypocalcemia, and calcium and vitamin D were replaced orally. Postoperative exams: calcium = 8.2 mg/dL and iPTH = 24 pg/mL. Bone densitometry one year after surgery was as follows: radius 33 = 0.449 g/cm^2 (-4.43); L2-L4 = 0.810 g/cm^2 (-3.58); femoral neck = 0.687 g/cm^2 (-3.19). That evidenced an increase in bone mass of 10% in radius 33, 4% in L2-L4, and 60% in the femoral neck.

Case 3: The patient is a 38-year-old white female reporting orthopedic surgery due to a tumor in her left tibia (histopathology: aneurysmatic bone cyst) four years earlier. Later, the patient had a fracture and a radiological image suggesting brown tumor in the previously affected limb, and kidney stones. The laboratory exams were as follows: serum calcium = 11.9 mg/dL; P = 1.9 mg/dL; iPTH = 1,268 pg/mL; alkaline phosphatase = 2,821; 24-hour calciuria = 327 mg/24 h; UDPD = 22.5 nmol/mmol of creatinine. Bone densitometry: radius 33 = 0.264 g/cm^2 (-6.31 SD); L2-L4 = 0.530 g/cm^2 (-5.59 SD); femoral neck = 0.234 g/cm^2 (-6.22 SD). The patient underwent parathyroidectomy (histopathology: parathyroid adenoma), and received 90 mg of pamidronate 24 hours prior to surgery. Postoperative exams: calcium = 8.2 mg/dL; PTH = 2.8 pg/mL. Bone densitometry one year after parathyroidectomy: radius 33 = 0.347 g/cm^2 (-5.14 SD); L2-L4 = 0.877 g/cm^2 (-2.69 SD); femoral neck = 0.541 g/cm^2 (-3.68 SD). That evidenced an increase in bone mass of 32% in radius 33, 65% in L2-L4, and 131% in the femoral neck.

Case 4: The patient is a 42-year-old female reporting a tumor in the anterior side of her left leg two years earlier. In an orthopedic service, she underwent excision of the tumor, whose histopathological diagnosis was giant cell tumor. In the following year, she noticed the appearance of tumors in her forearm and right leg, whose biopsy revealed brown tumor. Laboratory exams: CTX = 2,160 pg/mL; iPTH = 1,040 pg/mL; serum calcium = 13.7mg/dL; 25-hydroxyvitamin D (25OHD) = 10 ng/mL; P = 2.0 mEq/L. Radiography of the skull showed the "salt and pepper" image of the skullcap. The radiography of her upper limbs showed a lytic lesion in the distal third of her right ulna, and that of her lower limbs showed a lytic lesion in the middle third of her right tibia. Bone densitometry: L2-L4 = 0.582 g/cm² (-5.15 SD) and femoral neck = 0.565 g/cm² (-3.45 SD). Technetium-99m-Sestamibi scintigraphy: increased uptake in the left upper parathyroid. Oral alendronate, 140 mg/week for six weeks, was started. The patient underwent left lower parathyroidectomy (histopathology: parathyroid adenoma) and left thyroid lobectomy after transoperative gamma-detection probe use. After one week, the patient had mild hypocalcemia. Postoperative exams: UDPD = 29.2 nmol/mmol of creatinine; iPTH = 40 pg/mL; serum calcium = 8.3 mg/dL. Treatment with oral calcium and vitamin D3 was started. Bone densitometry one year after surgery: L2-L4: 0.940 g/cm^2

(-2.16 SD), and femoral neck: 0.942 g/cm^2 (-0.32 SD). That showed a bone mass increase of 61% in L2-L4, and of 66.7% in the femoral neck.

Case 5: The patient is a 52-year-old female reporting that six years earlier she began to experience pain and cramps in her legs, polyarthralgia, and back pain. The laboratory exams showed serum calcium of 13.6 mg/dL and iPTH of 1,193 pg/mL, and she was diagnosed with PHPT. Bone scintigraphy showed an increased diffuse uptake in the axial and appendicular skeleton, a scintigraphic pattern compatible with hyperparathyroidism. The patient refused to undergo parathyroidectomy. One year later, a fracture in her right femur was diagnosed and she underwent surgery. Four years later, the patient had a fracture in her right shoulder, and sought medical advice. Laboratory exams: serum calcium = 14.3 mg/dL; PTH = 1,588 pg/mL; CTX = 4,050 pg/mL. Radiography of her skull showed the "salt and pepper" pattern in the skullcap. Radiography of her lower limbs showed osteoclastomas in her right and left femurs and in her left knee. Bone densitometry: L2-L4 = -2.48 SD (0.882 g/cm²), femoral neck = -5.7 DP (0.639 g/cm²), and radius 33 = -5.96 (0.288 g/cm²). Cervical ultrasound revealed a solid hypoechoic nodule measuring 3.8 cm in its greater diameter, suggestive of a solid nodule of the right lower parathyroid. Tc-99m-Sestamibi scintigraphy showed a nodular area of intense anomalous hyperconcentration of the tracer in the anterior cervical region (topography of the right thyroid lobe and/or right parathyroid). In addition, areas of hyperconcentration of the tracer in the middle third of her left thigh and in her left knee were observed. Treatment with oral alendronate, 140 mg/week for six weeks, was started. Right lower parathyroidectomy was performed (histopathology: parathyroid adenoma). One week after surgery, the patient had mild hypocalcemia (paresthesia and cramps). Postoperative exams: iPTH = 192 pg/mL; calcium = 8.5 mg/dL. The patient was discharged from the hospital asymptomatic and with a prescription of oral calcium and vitamin D3.

Case 6: The patient is a 25-year-old male reporting that three years earlier he began experiencing arthralgia in his left knee, which evolved to pain in his legs, causing walking limitation. The laboratory exams showed iPTH = 2,498 pg/mL; serum calcium = 13.2 mg/dL; P = 2.0 mEq/L; CTX = 1,669 pg/mL; 25OHD = 10.4 ng/mL; alkaline phosphatase = 1,314 U/L; 24-hour calciuria = 50 mg/24 h. The radiography suggested osteoclastoma (brown tumor) in the distal region of his left femur, and the "salt and pepper" pattern in his skullcap. The cervical ultrasound showed a solid hypoechoic nodule in his right lower thyroid lobe, of approximately 3.6 × 2.2 cm. The ultrasound of the kidneys and urinary tract revealed bilateral kidney stones. Full-body Sestamibi scintigraphy evidenced focal uptake in the lower pole of the right thyroid lobe, suggestive of right lower parathyroid adenoma. Bone densitometry: radius 33 = 0.320 g/cm^2 (-6.03 SD); L1-L4 = 0.750 g/cm^2 (-3.9 SD); femoral neck = 0.523 g/cm^2 (-4.2 SD). Ibandronate, 150 mg, was administered ten days prior to surgery. The patient underwent right lower parathyroidectomy (histopathology: parathyroid adenoma). Laboratory exams 24 hours after surgery: iPTH = 11.07 pg/mL; Ca = 8.8mg/dL; and albumin (Alb) = 4.1. After surgery, treatment with calcium and vitamin D was started. Six months after surgery, the laboratory exams were as follows: Ca = 9; Alb = 3.8; CTX = 636 pg/mL; and 25OHD = 33 ng/mL. Bone densitometry performed six months after surgery: radius 33 = 0.444 g/cm^2 (-5.6 SD); L1-L4 = 0.954 g/cm^2 (-2.3DP); femoral neck = 0.707 g/cm^2 (-2.8 SD). That showed a bone mass increase of 38.7% in radius 33, 27.2% in L1-L4, and 35.1% in the femoral neck.

RESULTS

Six patients with confirmed diagnosis of OFC (three women; mean age, 35.6 ± 10.5 years; age range, from 25 to 52 years) were assessed.

The initial means and standard deviations of the laboratory parameters were as follows: serum calcium = 13.51 ± 0.87 mg/dL; P = 2.01 ± 0.52 mg/dL; iPTH = 1.389 ± 609 pg/mL; alkaline phosphatase = 1,918 ± 1,070 U/L; 24-hour calciuria = 221 ± 106 mg/24h; UDPD = 131 ± 183 nmol/mmol of creatinine; and CTX = 2,253 ± 1,587 pg/mL.

The initial, post-bisphosphonate, and immediately postoperative serum calcium levels of all patients are shown in Table 1.

The initial and post-bisphosphonate values of bone markers of all patients are shown in Table 2, in which the following are seen: a decrease in UDPD levels (nmol/mmol of creatinine) of 53% in case 1 and of 51% in case 2; a decrease in CTX levels (pg/mL) of 38% in case 4; and an increase in CTX levels (pg/mL) of 15% in case 5.

None of the patients showed signs of hypocalcemia in the first postoperative week: their mean serum level of calcium was 8.23 ± 0.46 mg/dL, and their postoperative iPTH level was 45.8 ± 72.9 pg/mL.

The mean initial bone densitometry (T-score) was as follows: 0.673 ± 0.150 g/cm^2 (-4.42 ± 1.23 SD) in L2-L4; 0.456 ± 0.149 g/cm^2 (-5.58 ± 1.79 SD) in femoral neck; and 0.316 ± 0.055 g/cm^2 (-5.85 ± 0.53 SD) in radius 33. One year after parathyroidectomy, four patients underwent a new bone densitometry. In case 5, the exam was repeated after six months.

Tables 3, 4, and 5 show the bone mineral densities initially and one year after surgery of four patients, as well as the bone mass gain in the three areas analyzed. Increases in bone mineral density of 40% ± 29% in L2-L4, of 86% ± 39% in the femoral neck, and of 22% ± 11% in radius 33 were observed.

Table 1
Serum calcium levels before and after the use of bisphosphonates and immediately after parathyroidectomy in the six patients studied

Patient	Initial calcium (mg/dL)*	Post-bisphosphonate calcium **	Postoperative calcium***
Case 1	14.0	11.6	7.4
Case 2	15.0	11.0	8.2
Case 3	11.9	–	8.2
Case 4	13.7	12.3	8.3
Case 5	14.3	14.1	8.5
Case 6	13.2	12.3	8.8

*: measured 24 hours prior to beginning bisphosphonates; **: measured 24 hours after finishing bisphosphonates; ***: measured 24 hours after parathyroidectomy.

Table 2
Variation in the levels of bone resorption markers after using bisphosphonates in the six patients studied

Patient	Bone markers	Initial	Post-bisphosphonate	Level variation
Case 1	UDPD	342	160	-53%
Case 2	UDPD	28.8	14	-51%
Case 3	UDPD	22.5	–	–
Case 4	CTX	2,160	1,340	-38%
Case 5	CTX	4,050	4,950	+15%
Case 6	CTX	1,669	636	-62%

UDPD: urine deoxypyridinoline (nmol/mmol of creatinine); ¨CTX: serum C-telopeptide (pg/mL). Bone resorption markers were measured 24 hours before beginning the bisphosphonates and 24 hours after ending their use.

Table 3
Percentage variation in the bone mineral density of the lumbar spine of five patients after parathyroidectomy

Patient	BMD (g/cm²) initial	BMD (g/cm²) 6 months	BMD (g/cm²) 1 year	BMD gain
Case 1	0.517	–	0.673	30%
Case 2	0.779	–	0.810	4%
Case 3	0.530	–	0.877	65%
Case 4	0.582	–	0.940	61%
Case 5	–	–	–	–
Case 6	0.750	0.954	–	27%

MD: bone mineral density.

Table 4
Percentage variation in the bone mineral density of the femoral neck of four patients after parathyroidectomy

Patient	BMD (g/cm²) initial	BMD (g/cm²) 6 months	BMD (g/cm²) 1 year	BMD gain
Case 1	0.350	–	–	–
Case 2	0.430	–	0.687	60%
Case 3	0.234	–	0.541	131%
Case 4	0.565	–	0.942	67%
Case 5	–	–	–	–
Case 6	0.523	0.707	–	35%

BMD: bone mineral density.

Table 5
Percentage variation in the bone mineral density of radius 33 of four patients after parathyroidectomy

Patient	BMD (g/cm²) initial	BMD (g/cm²) 6 months	BMD (g/cm²) 1 year	BMD gain
Case 1	0.303	–	0.384	26%
Case 2	0.409	–	0.449	10%
Case 3	0.264	–	0.347	32%
Case 4	–	–	–	–
Case 5	–	–	–	–
Case 6	0.320	0.444	–	38%

BMD: bone mineral density.

DISCUSSION

The results of this study suggest that the bisphosphonate use in patients with PHPT and OFC is safe and can be considered effective to minimize severe hypocalcemia secondary to the bone hunger syndrome already demonstrated in the postoperative period of parathyroidectomy of patients with severe PHPT.[4,7]

So far, there is no recommendation for using bisphosphonates in patients with PHPT. A study carried out in Taiwan with 23 patients using pamidronate (doses ranging from 60 to 90 mg) has suggested that bisphosphonates can prevent bone hunger after parathyroidectomy.[12] However, considering the lower prevalence of that complication in asymptomatic patients, bisphosphonates seem to be more useful in those with more severe conditions and high bone remodeling. Literature data about OFC, however, are scarce, and data about the use of bisphosphonates in those patients have not been found.

There are, however, reports on the use of pamidronate to prevent bone hunger syndrome in patients with asymptomatic hyperparathyroidism. The first report was about a 62-year-old woman, who used pamidronate at the dose of 60 mg prior to surgery and had no postoperative hypocalcemia.[13] The second report was about a 73-year-old woman with serum calcium of 12.2 mg/dL in the preoperative period, who received a cumulative dose of pamidronate of 90 mg and showed serum calcium of 9.8 on the first postoperative day.[14] In our case series, only one female patient used pamidronate. The most used bisphosphonate was alendronate, but we could not find other data in the consulted literature about its use to prevent bone hunger in patients with hyperparathyroidism associated with OFC.

We observed a reduction in the serum levels of calcium after using bisphosphonates, and no hypocalcemia with their use. Chow *et al*.[15] have reported that asymptomatic and post-menopausal women with PHPT, after 48 weeks using 10 mg/day of alendronate, showed a moderate and significant reduction in their serum levels of calcium, with no change in the serum PTH concentration.

Bilezikian *et al*.[16] have shown a significant reduction (66%) in the levels of the bone remodeling marker urine NTX three months after treatment with alendronate, 10 mg/day, in patients with asymptomatic PHPT. Table 4 shows 53% and 51% reductions in UDPD levels in two patients, a result similar to those of some publications.[16,17] One patient had a 38% reduction in CTX levels after using 140 mg/week of alendronate for six weeks, but another female patient had a 15% increase in CTX after using alendronate. It is worth emphasizing that the interassay variability in the serum measurement of beta-CTX is 10%-15%; thus, we can conclude that the CTX levels of that female patient remained stable after using alendronate, which could have resulted from the long course and severity of her disease diagnosed six years prior to that preoperative treatment.

Bibliographic data about the use of bisphosphonates in patients with asymptomatic PHPT have shown a moderate reduction in serum calcium, while PTH did not change two years after treatment with alendronate.[14] Those studies have also confirmed a bone mass gain on bone densitometry, suggesting that alendronate is an alternative treatment for asymptomatic PHPT with no surgical indication.[15,17] Almost all patients with OFC have severe hypocalcemia due to bone hunger syndrome, and, after normalizing serum PTH on the first postoperative day, they usually require high doses of vitamin D and calcium supplementation to prevent hypocalcemia permanence for several months after surgical cure.[4,7] Our patients had mild hypocalcemia during the first postoperative week, requiring oral replacement of calcium carbonate and vitamin D3. Thus, bisphosphonates seem to attenuate severe hypocalcemia in the postoperative period of patients with OFC.

The use of bisphosphonates, especially at high doses, in patients with severe PHPT could reduce the intense bone remodeling existing prior to parathyroidectomy. That effect would, thus, be felt after surgery, decreasing the velocity of calcium influx to the bone, preventing its sudden drop and the symptoms of severe hypocalcemia. Considering, then, that bone hunger is more prevalent and worrying in patients with the severe form of the disease (due to their more intense bone remodeling) than in asymptomatic patients, the use of bisphosphonates should be reserved only for the former. Further studies are, however, required to support that recommendation.

We demonstrated that the preoperative use of bisphosphonates in patients with OFC did not prevent the increase in bone mass that occurs after parathyroidectomy in the three sites assessed. In addition, the mean gain in bone mineral density one year after surgery in four patients was 40% ± 29% in L2-L4, 86 ± 39% in the femoral neck, and 22% ± 11% in radius 33. The most evident bone mass gain occurred in the femoral neck, reaching up to 131% in one of the patients, and the site with the lowest gain was radius 33. In case 6, an important increase in bone mass in the three sites assessed was evidenced as early as six months after surgery.

According to Bilezikian *et al*.[18,19], a long-term follow-up of patients with PHPT undergoing surgery has revealed a bone mass gain of 10%-12% in L2-L4 and femoral neck within a 10-year period following parathyroidectomy. Nomura *et al*.,[20] studying a Japanese population with PHPT undergoing parathyroidectomy, have reported a sustained increase in bone mass both in L2-L4 and radius 33 over a 6-year period. Parker *et al*.[17] have reported a 7.3% ± 1.7% bone mass gain in L2-L4 after one year of treatment with alendronate in patients with PHPT and osteoporosis, who did not undergo parathyroidectomy.

No data have been published about the effect of bisphosphonates on bone mass gain in patients with OFC. However, two randomized studies with 66 women with asymptomatic PHPT treated with alendronate and not undergoing parathyroidectomy have shown an increase in bone mineral density of 3.7%-5% in L2-L4 and of 2%-4.2% in the femoral neck; in distal radius, however, no significant increase in bone mass was observed.[21]

Our study had some limitations. Firstly, it was a retrospective study, with no control group for comparison and a small number of patients assessed. Because it was a review of medical records, including patients followed up in different periods of time, and without a protocol determining the dose and the salt of bisphosphonate to be used, there was no homogeneity in the treatment of patients (different salts, different doses, and different administration routes). Drug availability was the major determinant of the type of treatment chosen for each patient. Studies with a larger number of patients, using preferably the same bisphosphonate salt at standardized doses, should, thus, be carried out.

In conclusion, therapy with bisphosphonates before parathyroidectomy seems to be effective in reducing bone remodeling and in attenuating severe hypocalcemia consequent to bone hunger syndrome in the postoperative period of patients with OFC. In addition, the use of bisphosphonates does not prevent the marked increase in bone mass observed during the follow-up of those patients.