

Altered Calcium Metabolism in Patients on Long-term Bisphosphonate Therapy for Metastatic Breast Cancer

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Abstract. *Background:* Bisphosphonates (BPs) are considered the standard of care in metastatic breast cancer (MBC) patients with bone metastases. Because the survival for these patients may be prolonged compared with those patients with visceral metastases, they may be prescribed BPs for several years. The effects of this long-term BP use on calcium metabolism in MBC patients have not previously been described. *Objectives:* The main objective of this study was to evaluate the effect of long-term BP use on calcium homeostasis in MBC patients. The secondary objective was to assess Vitamin D levels in these patients. *Materials and Methods:* An exploratory analysis of serum calcium, parathyroid (PTH), and 25 hydroxycholecalciferol (25-(OH)D) levels and their inter-relationships was undertaken in 46 MBC patients who had been on prolonged BP therapy. These results were compared to a historical control group of 420 patients without bone or mineral disease who were matched for gender, age, baseline renal function and season of seological testing. *Results:* Patients were similar in the two groups with no significant difference in mean age, baseline creatinine or season of testing. Serum calcium was no different between the two groups. However, PTH was significantly higher in MBC patients, compared to controls (5.7 vs. 4.8 pmol/L, $p=0.043$). Linear regression analysis showed that PTH was significantly higher in the MBC group at lower serum calcium levels and fell sharply with increasing serum calcium levels ($p=0.0001$). Among the patients with MBC, 62% had suboptimal levels of vitamin D

and 18% were found to have insufficient or deficient levels (25-(OH)D < 40nM) despite taking dietary supplementation. *Conclusion:* In MBC patients with prolonged BP use, there appears to be a state of hyperparathyroidism similar to that seen with BP use in benign bone disease. Supplementation with 400 IU per day of Vitamin D per day was not sufficient to correct this metabolic abnormality.

Calcium homeostasis is a well-coordinated regulatory mechanism involving the parathyroid glands, kidneys, intestine and bone. This complex, tightly controlled system relies on appropriate sensing of ionized calcium levels in the blood via the calcium-sensing receptor in the parathyroid and kidney. This, in turn, signals appropriate release of parathyroid hormone (PTH), which among other actions promotes the renal cortical conversion of the 25 hydroxycholecalciferol (25-(OH)D) precursor to the active hormone, 1,25-dihydroxycholecalciferol (1,25-(OH)₂D₃) or calcitriol. Calcitriol then stimulates calcium uptake from the intestine and activation of bone turnover (1).

In malignancy, the balance is altered through several mechanisms. At any disease stage, release of parathyroid hormone-related peptide (PTHrP) by cancer cells can result in hypercalcemia (2). In the setting of metastatic cancer to bone, this system is further altered, leading to a vicious cycle of growth factor release by tumor cells, stimulating osteoclastic activity, and leading to bone breakdown and further liberation of calcium into the bloodstream (2). This release of calcium leads to the physiological suppression of endogenous PTH and reduces calcitriol synthesis (3).

The management of patients with bone metastases has been revolutionized by the use of bisphosphonates (BPs). The BPs are synthetic analogs of pyrophosphate which inhibit osteoclastic activity thereby decrease bone turnover. They exert their effects directly, by hindering recruitment and function of osteoclasts, and indirectly, by stimulating osteoblasts to produce inhibitors of osteoclast formation. These agents have been proven to be effective in the

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Table I. Baseline characteristics of MBC and control group patients.

Variable	Metastatic breast cancer (n=46)	Control group (n=420)	P-value
Age (years)			
Mean	57.6	59.7	0.285
Std dev	12.4	12.6	
Median	59.5	59.1	
Serum creatinine (μmol/L)			
Mean	67.3	69.9	0.245
Std dev	14.7	12.2	
Median	66.5	68	
Season			
Winter	19 (41.3%)	148 (35.2%)	0.416
Summer	27 (58.7%)	272 (64.8%)	
Baseline KP Score			
Mean	87.4	-	-
Median	90	-	
Duration bone mets (months)			
Mean	30.8	-	-
Median	21	-	
Duration of BP use (months)			
Mean	19.9	-	-
Median	15.3	-	
BP used			
Clodronate	11 (23.9%)	-	-
Pamidronate	35 (76.1%)	-	

treatment of osteoporosis, Paget's disease of bone, hypercalcemia of malignancy and in the treatment of bone metastases (4).

BPs have become the standard of care in the treatment of metastatic bone lesions in breast cancer patients (5, 6). These agents are typically prescribed at the first evidence of bony metastases, and then continued, sometimes indefinitely, even in the presence of progressive disease. While the short-term effects of BPs on calcium levels in this population have been extensively described (7), there are few data in the literature exploring the effects of chronic use of BPs on calcium homeostasis in cancer patients. In Paget's disease of bone, secondary hyperparathyroidism induced by chronic oral BP use has been described and presumably relates to the induction of transient hypocalcemia by BPs (8). This has been shown to be preventable through the administration of calcium (1.0-1.2 g/day) and vitamin D (equivalent to 500 IU/day of vitamin D₃) supplementation in this population (9). Such observations have not been reported with long-term use of BPs in the breast cancer literature, and recommendations of calcium and vitamin-D supplementation in this patient population appear to be based on sparse literature. Indeed, a review from the Memorial Sloan Kettering Cancer Centre revealed that less than 37% of breast cancer patients take calcium or vitamin-D supplements, despite nutritional counseling (10).

Table II. Calcium and parathyroid hormone levels in MBC and control group patients.

	MBC (n=46)	Control group (n=420)	P-value
Calcium (mmol/L)			
Mean	2.38	2.38	0.680
Std error	±0.01	±0.005	
Parathyroid hormone (pmol/L)			
Mean	5.67	4.80	0.043
Std error	±0.40	±0.12	

Table III. Vitamin-D status in MBC and control group patients.

Vitamin-D status	MBC patients (n=46)	Control group patients (n=420)	P-value
Optimal (>70 nmol/L)	17 (38%)	93 (22.1%)	0.023
Suboptimal (40-70 nmol/L)	20 (44%)	236 (56.2%)	
Insufficient (20-39 nmol/L)	7 (16%)	78 (18.6%)	
Deficient (<20 nmol/L)	1 (2%)	13 (3.1%)	

Recently, there has been a trend towards increased use of BPs, not only in the metastatic setting, but also in the adjuvant setting for the prevention of aromatase inhibitor-induced bone loss, as well as for the primary prevention of bone metastases in breast cancer survivors (11, 12). It is therefore, important not only to study the long-term effects of BPs on calcium homeostasis but also to develop more appropriate recommendations for calcium and vitamin D supplementation. The primary objective of this study was to determine if patients with metastatic breast cancer (MBC) on chronic BPs had alteration in serum calcium-PTH relationship compared to controls. The secondary objective was to assess vitamin D levels in this population compared to normal controls.

Materials and Methods

An exploratory analysis of calcium, PTH, 25-(OH)D, and their interrelationships was performed on 46 breast cancer patients with bone metastases who were enrolled in at least one of two phase II studies exploring the use of either zoledronic acid (4 mg intravenously, monthly) or ibandronate (5 mg orally, daily). All patients were established on BP therapy (*i.e.* either intravenous pamidronate or oral clodronate) prior to entry into the trials. Patients had experienced either a skeletal related event (SRE) or progressive bone metastases while on this therapy (13, 14). For patients enrolled in both studies, data was used from the first study they participated in. Patients were excluded if biochemical data acquisition was incomplete. Further inclusion criteria included good performance status (Karnofsky Performance Status (KPS) >60) and a life expectancy of at least 3 months. Patients were excluded if they had

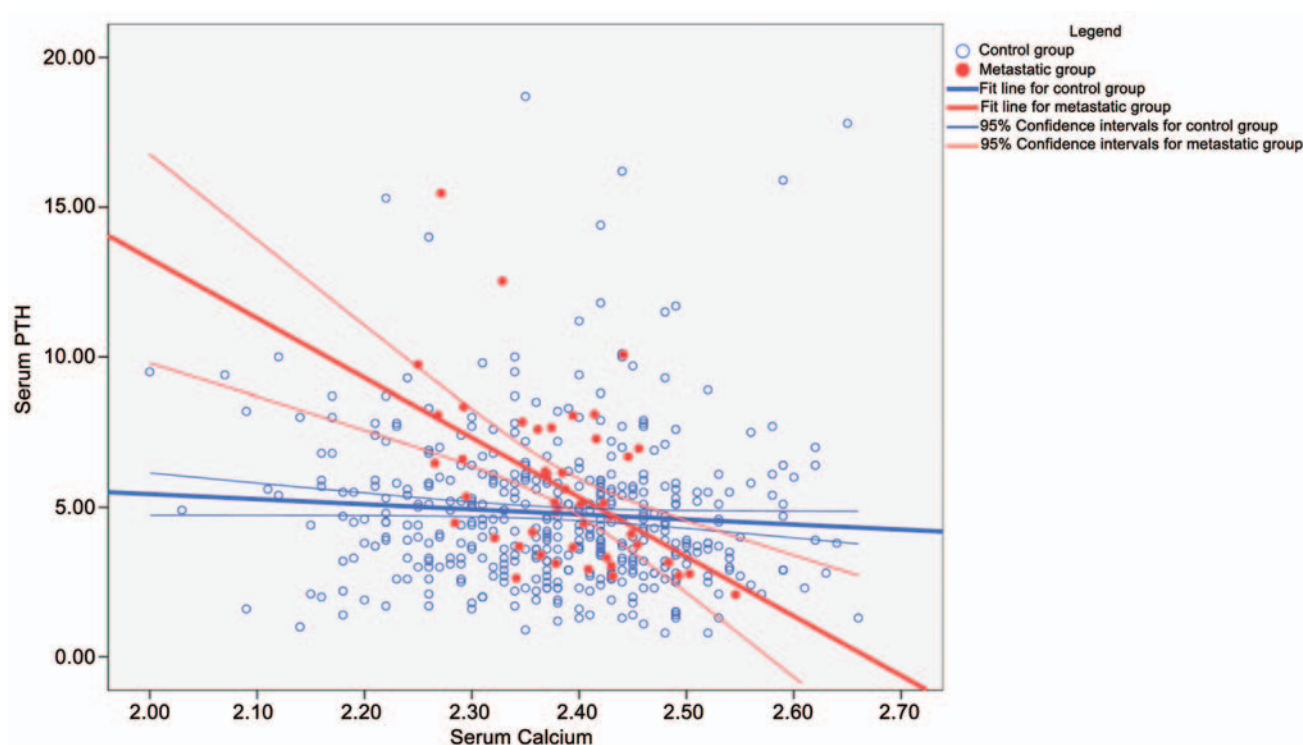


Figure 1. Linear Regression of serum Calcium (mmol/L) and PTH (pmol/L).

a change in systemic anticancer treatment in the month before or after enrollment into the study. Patients with an acute pathological fracture, spinal cord compression, hypercalcemia, prior hypersensitivity to bisphosphonates or severe renal or hepatic dysfunction were also excluded from the study. All patients received calcium carbonate and 25-(OH)D supplementation at doses of 1 gram and 400 IU per day, respectively, for one month prior to any serological testing.

Serum samples from these 46 patients were collected at baseline prior to initiation of zoledronic acid or ibandronate treatment. Serum was tested for calcium, albumin, PTH, 25-(OH)D and creatinine. Serum calcium was collected and analyzed and was then corrected for serum albumin. Sample handling for PTH involved drawing blood in the morning to avoid any diurnal variation and analyzing the samples immediately. Samples were not stored and batched tested. The laboratory reference range, which was used for PTH, was 1.7 to 7.6 pmol/L. Intra- and inter-assay coefficients of variation were less than 3%.

Corrected calcium, PTH and 25-(OH)D levels in these patients were compared to the same biochemical parameters obtained from a historical control group of 420 patients who were matched for age, gender, baseline creatinine and season of testing. This historical control group, which was selected from patients enrolled in an epidemiological study of correlation between age, 25-(OH)D and PTH (15) consisted of patients with no evidence of breast cancer or bone disease. Furthermore, none were receiving prior therapy with BPs or vitamin D. Both the study group and the historical control group underwent testing by the same routine biochemical analytical methods.

In order to assess differences between the metastatic breast

cancer and control groups, the following statistical tests were utilized: Student's *t*-test was used to compare the variability in means of parametric data (calcium, PTH, and 25-(OH)D). The Mann-Whitney test was used for comparing non-parametric variables (season of testing). For serum calcium/PTH inter-relationship, linear regression analysis was performed. For comparative purposes, vitamin D levels were stratified into the following categories: *vitamin D deficiency* was defined as serum 25-(OH)D level <20 nmol/L; *vitamin D insufficiency* was defined as serum 25-(OH)D level of 20-40 nmol/L, *suboptimal vitamin D* was defined as serum 25-(OH)D level of 41-75 nmol/L, and *optimal vitamin D* was defined as 25-(OH)D level >75 nmol/L. All statistical analyses were performed using SPSS (version 13) statistical software (SPSS Inc., Chicago, IL, USA).

The Research Ethics Board of Sunnybrook Health Sciences Centre approved both the phase II studies from which MBC data was collected as well as access to retrospective patient data for the control group.

Results

Baseline characteristics in the MBC group were not significantly different from those of the historical control group (Table I). All patients in both groups resided in the same geographical area (Toronto, Canada), with exposure to similar amounts of sunlight and the same general climate. In the study group, the mean duration of prior bisphosphonate therapy was 19.9 months (median 15.3 months). Most

patients (76.1%) had received prior intravenous pamidronate, while the rest were previously treated with oral clodronate.

Mean serum calcium was not significantly different between the MBC and control groups. However, PTH was significantly higher in patients with MBC compared to controls (Table II). Linear regression analysis showed that PTH was significantly higher in the MBC group at lower serum calcium levels and fell sharply with increasing serum calcium levels (Figure 1). Despite supplementation with 400IU of vitamin D daily, 62% of MBC patients had suboptimal levels of 25-(OH)D (Table III). Of these, 18% had either insufficient or grossly deficient levels.

Discussion

The importance of calcium and vitamin D in pathogenesis and progression of breast cancer has been demonstrated by *in vitro* studies (16-18), animal studies (18, 19), and in population epidemiological studies, which show a higher incidence of breast cancer in patients living at higher latitudes where lower levels of ultraviolet radiation would be expected to be associated with reduced cutaneous synthesis of vitamin D (20, 21). In addition, lower measured levels of 25-(OH)D have been shown to correlate with poor prognosis (22, 23).

Despite the emerging evidence base supporting the utility of vitamin D and calcium in untreated breast cancer, there unfortunately remains very little data to support its use in patients with metastatic bone disease treated with BPs. Calcium and vitamin D metabolism is especially important in the context of metastatic breast cancer affecting bones. The long-term use of bisphosphonates has been shown to cause altered calcium metabolism in patients with both osteoporosis and Paget's disease of bone. These alterations predominantly include hypocalcemia and resultant secondary hyperparathyroidism. Consequently, it has been recommended that clinicians supplement calcium and vitamin D in BP therapy (24). In metastatic cancer, supplementation has been recommended based on extrapolation from data derived from a population with benign bone disease.

In this study, it was shown that patients with MBC had higher levels of PTH than those of the control group, despite similar serum calcium levels. Furthermore, regression analysis showed that at lower levels of serum calcium, patients with MBC had significantly higher levels of PTH than expected based on comparison with the control group. This increase in PTH may be explained by emergence of a secondary hyperparathyroidism similar to that shown after BP therapy in benign bone disease (24). Possible explanations for the steep fall in PTH levels with rising calcium levels is the physiological suppression of its release due to increasing release of calcium into the bloodstream by lytic metastases, although a disturbance in the negative

feedback of calcium on the parathyroid hormones *via* the calcium-sensing receptor is also possible (25).

Of interest, all patients in this study were treated with 400 IU of vitamin D daily for at least one month prior to enrollment. This dose was previously shown to reduce the incidence of secondary hyperparathyroidism in patients with benign bone disease. It would appear that in a group of patients with MBC, such levels of vitamin D supplementation are not sufficient for correction of hyperparathyroidism and indeed only 38% of patients were found to have optimal levels of vitamin D.

The implications of such findings are multiple. Firstly, patients suffering from primary hyperparathyroidism are known to develop symptoms including malaise, decreased energy, and generalized pain. These symptoms are similar to those frequently described by breast cancer patients with bone metastases. It is therefore possible that the hyperparathyroid state may be contributing in some way to these subjective findings. Methods to ameliorate this disturbance in calcium and PTH may therefore be of some use in the palliation of symptoms.

Secondly, it is known that high PTH levels increase the degree of vitamin D activation. This, in turn, stimulates calcium absorption, raises calcium serum levels, and results in negative feedback shutdown of PTH release. In the osteoporosis literature, the hyperparathyroidism induced by chronic BP use has been demonstrated to improve in response to vitamin D supplementation. It has also been demonstrated that patients with more advanced breast cancer have increased deficiency in vitamin D (22, 23). It would therefore appear that the dosing of 25-(OH)D used in this study was insufficient to overcome the relative deficiency that these patients had. Increased supplementation with vitamin D may suppress the observed hyperparathyroidism and reduce patient symptoms. Consequently, local recommendations for 25-(OH)D supplementation have been increased to at least 1,000 IU daily.

In view of the exploratory nature of the analysis of this study, the generalization of results is limited to patients who experienced either an SRE or progressive bone metastases while on BP therapy. A second limitation of this study is that the reference group MBC patients were compared to was a historical control group. While all biochemical analyses were performed using the same techniques, the limitation inherent in comparisons to such a control group remain.

In summary, this study has described the effect of long-term BP use on calcium metabolism in MBC patients. It has been shown that patients with MBC appear to have an apparent disturbance in the homeostatic relationship between calcium and PTH, which results in the emergence of a secondary hyperparathyroidism similar to that found in patients on long-term BPs for benign bone disease. In addition, it has been shown that these patients remain deficient in vitamin D despite

dietary supplementation. Further studies may assess if adequate correction of this deficiency could restore normal calcium metabolism in these patients and improve patient symptoms.

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