Biochemical Response to Treatment of Bone Hyperresorption in Chronically Critically Ill Patients*

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Study objective: The chronically critically ill (CCI) are a subgroup of critically ill patients who have survived an acute critical illness but remain profoundly debilitated and ventilator dependent. We have previously shown that CCI patients have a very high prevalence of bone hyperresorption. The objective of this present study was to determine the biochemical response of bone hyperresorption in CCI patients to treatment with either calcitriol alone or calcitriol and pamidronate.

Design: Retrospective survey.

Setting: Respiratory care step-down unit (RCU) at a tertiary-care teaching hospital.

Patients: Fifty-five ventilator-dependent CCI patients transferred from ICUs within the same institution who had elevated urine N-telopeptide (NTx) levels at RCU admission, who were treated with either calcitriol alone (n = 44) or calcitriol and pamidronate (n = 11), and who had urine NTx levels remeasured following treatment.

Intervention: None.

Measurements and results: Patients treated with calcitriol alone had a significant reduction in serum parathyroid hormone (PTH; 93 ± 145 pg/mL vs 40 ± 28 pg/mL; p = 0.02) but not in urinary NTx (187 ± 146 nmol bone collagen equivalents [BCE]/mmol creatinine [Cr] vs 178 ± 123 nmol BCE/mmol Cr, p = 0.59). In contrast, patients treated with both calcitriol and pamidronate had a significant decrease in urine NTx at follow-up (329 ± 238 to 100 ± 85 nmol BCE/mmol Cr; p < 0.01) but not in serum PTH (36 ± 29 to 53 ± 51 pg/mL; p = 0.44).

Conclusion: The bone hyperresorption of CCI patients is PTH independent and biochemically responds to treatment with calcitriol and pamidronate but not calcitriol alone.

Key words: bed rest, adverse effects; calcitriol; chronic disease; critical illness, rehabilitation; diphosphonates; epidemiology; osteoporosis; parathyroid hormones, blood; risk factors; ventilator weaning; vitamin D deficiency

Abbreviations: BCE = bone collagen equivalents; CCI = chronically critically ill; CCU = cardiac care unit; Cr = creatinine; CSICU = cardiothoracic surgery ICU; IL = interleukin; MICU = medical ICU; NSICU = neurosurgical ICU; NTx = N-telopeptide; PTH = parathyroid hormone; RCU = respiratory care unit; SICU = surgical ICU

Most patients admitted to ICUs either recover or die within the first few days of the onset of critical illness. However, a subgroup of critically ill patients enters a more prolonged phase, with a continuing need for mechanical ventilation and intensive nursing care that may last for weeks to months. These patients have been termed, chronically critically ill (CCI).1-5 Treatment goals for CCI patients include the recovery of lost strength and function, liberation from mechanical ventilation, palliation of symptom burden, and minimization of acquired morbidities that may impact on their future level of function and quality of life.

In a previous study, we determined that during chronic critical illness, 92% of patients had abnormally increased urine N-telopeptide (NTx) levels diagnostic of accelerated bone destruction.1 We hypothesized that this bone hyperresorption was caused by a combination
of vitamin D deficiency and immobilization hyperresorption. In that study, 91% of CCI patients with bone hyperresorption had either elevated or inappropriately normal parathyroid hormone (PTH) levels, consistent with vitamin D deficiency.

In this study, we retrospectively review the biochemical response of CCI patients who have accelerated bone destruction to treatment with either 1,25-vitamin D alone or 1,25-vitamin D and the antiresorptive agent, pamidronate.

**Materials and Methods**

This study was approved by the Mt. Sinai School of Medicine Institutional Review Board. Medical records and laboratory data of all CCI patients admitted to the Mt. Sinai Hospital respiratory care unit (RCU) between March 1997 and October 1998 were retrospectively reviewed. CCI patients were defined as those ventilator-dependent ICU patients who had had elective tracheotomies performed specifically for failure to wean.

The RCU is a 15-bed step-down unit that accepts adult patients from the medical ICU (MICU), the surgical ICU (SICU), the cardiothoracic surgery ICU (CSICU), the neurosurgical ICU (NSICU), and the cardiac care unit (CCU). All patients admitted to the RCU must have a pulmonary physician as either their primary physician or as a consultant. However, daily patient care is provided by nurse practitioners in collaboration with primary attending physicians, and other consultants chosen by the primary physicians. As an open unit, each patient’s primary physician has discretion regarding which treatments to order, which consultations to request, and whether follow-up laboratory testing is to be done.

Patients were categorized by the acute event that led to prolonged mechanical ventilation, with a classification used by other authors. This classification includes six categories of diagnoses that lead to ventilator dependency: (1) chronic lung disease, (2) acute lung disease, (3) postoperative, (4) cardiac disease, (5) neurologic disease, and (6) other. If the reason for ICU admission was a major surgical procedure, the patient was categorized as a surgical patient; all other patients were identified as medical.

At RCU admission, all CCI patients were screened for bone hyperresorption as described below. Our study cohort was composed of CCI patients who, on retrospective review, had more than one urine NTx level determined during their RCU stay and who received treatment for bone hyperresorption between measurements. For patients with more than one RCU admission during the study period, only data from the first RCU admission were included.

**RCU Nutrition Support**

All patients admitted to the RCU received either enteral nutrition, parenteral nutrition, or a combination of both to achieve goals of 20 to 25 total kcal/kg/d and 1.2 to 1.5 g protein/kg/d titrated to clinical parameters, including serum BUN and ammonia levels, serial measurements of nitrogen excretion, liver function tests, metabolic cart measurements, and volume status. All patients received approximately 400 U vitamin D and 1,500 to 2,000 mg calcium/d, as part of either their enteral or parenteral nutrition. Calcium supplements were given to patients who were not receiving sufficient feeds and to patients with low initial urinary calcium levels that did not improve with calcitriol treatment.

**Laboratory Evaluations**

We have previously reported our bone hyperresorption screening procedures for CCI patients. Within 48 h of RCU admission, 24-h urine specimens were collected for urinary creatinine (Cr) and calcium levels, with measurements performed by the clinical laboratory of the hospital. Urine NTx levels were performed (Quest Diagnostics) using the Osteomark assay (Osteo International; Seattle, WA). This enzyme-linked immunosorbert assay uses a specific monoclonal antibody directed against the NTx intermolecular cross-linking domain of type I collagen of bone. Urine NTx values are then corrected for dilution by urinary Cr analysis and expressed as nanomoles of BCE per millimoles of Cr (normal range, 12 to 80 nmol BCE/mmol Cr). Urine NTx is a highly specific and sensitive assay of bone resorption, and is currently the only biochemical marker approved by the US Food and Drug Administration for this purpose.

Early morning blood samples were sent to the hospital clinical laboratory for measurement of total calcium, phosphorus, and albumin levels. Calcium was corrected for albumin levels using the following equation: calcium measured + [(40.0 – serum albumin) × 0.8]). All measurements were made with patients receiving continuous enteral and/or parenteral nutrition.

Intact PTH assays were performed by the hospital clinical laboratory using a solid-phase, two-site chemiluminescent enzyme immunoassay on an automated analyzer (Immulite Immunoassay Analyzer; Diagnostic Products; Los Angeles, CA), with reference range of 12 to 55 pg/mL and sensitivity of 1 pg/mL. 25-Vitamin D assays were performed (Lab Corp; Rariten, NJ) using a competitive protein binding assay (reference range, 16 to 74 ng/mL). 1,25-Vitamin D assays were performed (Lab Corp) using column chromatography and radioimmunoassay (reference range, 18 to 62 pg/mL).

**Treatment Protocols**

Based on the high prevalence of vitamin D deficiency found in our previous study, all patients with hyperresorption were treated with calcitriol (1,25-dihydroxyvitamin D₃), 0.25 μg/d enteraly or parenterally. Some patients also received pamidronate, 30 mg/d IV for 3 consecutive days. Pamidronate was used instead of other bisphosphonates because it can be given IV, has few side effects by the IV route, and can be intermittently dosed every 3 to 4 weeks. Pamidronate was recommended by the consultant endocrinologist based on individualized clinical and biochemical criteria, such as for patients with frank hypercalcemia or hypercalciuria. The final decision to use pamidronate was made by each patient’s primary physician.

**Statistical Analysis**

Laboratory data are shown as mean ± SD. All laboratory data were logarithmically transformed and then evaluated for normality using the Kolmogorov-Smirnov test, plots of means vs variance, and Levene’s test for homogeneity of variance. Distributions of all measured parameters were normally distributed. Continuous data between groups before and after treatment were analyzed using paired t tests. Correlations were performed using Pearson’s correlation coefficients. Categorical data were analyzed using the χ² test. The Kruskal-Wallis analysis of variance non-parametric test was used to compare durations of hospitalization prior to RCU admission and ages. All statistics were performed...
using computer software (Statistica for Windows, Release 5.0; StatSoft; Tulsa, OK). A p value using computer software (Statistica for Windows, Release 5.0; StatSoft; Tulsa, OK) was considered to be statistically significant.

Results

All CCI Patients

During the 19-month period reviewed, 157 CCI patients admitted to the RCU had baseline measurements of serum PTH, 25-vitamin D, and 1,25-vitamin D, and 24-urine collections for NTx and calcium levels. One hundred thirty-one patients (83%) had elevated urine NTx levels diagnostic of bone hyperresorption. Fifty-seven patients (36%) had follow-up urine NTx levels during their RCU stay. Two of these patients received no treatment for bone hyperresorption and were excluded from this analysis. One of these patients had an initial NTx of 305 nmol BCE/mmol Cr that increased to 742 nmol BCE/mmol Cr at follow-up. The other had an initial NTx level of 100 nmol BCE/mmol Cr that increased to 138 nmol BCE/mmol Cr. Both patients had initial PTH levels in the normal range.

Study Cohort

The remaining 55 patients (35% of total patients) comprise the final study cohort. Their median age was 75 years (range, 33 to 90 years), and included 30 men (55%) and 25 women (45%). Twenty-eight patients (51%) came from the MICU, 18 patients (32.7%) from the SICU, 5 patients (9.1%) from the CSICU, 2 patients (3.6%) from the NSICU, and 2 patients (3.6%) from the CCU. The primary reason for prolonged ventilator dependence was postoperative in 23 patients (42%), acute lung disease in 16 patients (29%), neurologic disease in 6 patients (11%), chronic lung disease in 8 patients (15%), and other medical diagnoses in 2 patients (4%). Four patients (7%) had metastatic cancer and 15 patients (27%) had received prolonged systemic corticosteroid treatment in the ICU before RCU admission. No patient required hemodialysis in the RCU. Thirty-one patients (56%) were categorized as medical and 24 patients (44%) were surgical, with a major operation as the primary reason for initial ICU admission. All patients had received nutritional support during their ICU stay.

The median duration of hospitalization before RCU admission was 22 days (range, 1 to 185 days), with a median ICU length of stay of 16 days (range, 1 to 177). There were significant correlations between urine NTx level and number of days in the ICU (r = 0.42, p < 0.01) and number of days in the hospital (r = 0.49, p < 0.01) before RCU admission.

Treatment Groups

All patients were treated with calcitriol between the first and second NTx measurements. Eleven patients (20%) also received pamidronate. No patient received more than one treatment with pamidronate during the period studied. Demographic data and selected baseline laboratory results for both treatment groups are shown in Table 1. The reasons for prolonged respiratory failure differed significantly between these groups, and patients who received calcitriol and pamidronate had significantly higher levels of serum calcium and urine NTx at baseline than those treated with calcitriol alone (Table 1). These biochemical differences reflect the clinical criteria used by the consultant endocrinologist when recommending that pamidronate be used.

PTH Response to Therapy

At baseline, PTH levels averaged 81 ± 123 pg/mL for all patients, with women having significantly higher PTH levels (124 ± 170 pg/mL) than men (44 ± 34 pg/mL; p = 0.01). Forty-one patients had baseline and follow-up PTH levels available for analysis. Patients (n = 35) treated with calcitriol alone had a significant reduction in PTH, from 93 ± 145 to 40 ± 25 pg/mL (p = 0.02). In contrast, patients treated with both calcitriol and pamidronate (n = 6) had PTH levels that rose from 36 ± 29 to 53 ± 51 pg/mL, which was not statistically significant (p = 0.44; Fig 1).

NTx Response to Therapy

Urine NTx levels averaged 215 ± 175 nmol BCE/mmol Cr for all patients at baseline. Follow-up NTx measurements were performed an average of 26 ± 12 days after the initial studies. Patients who had received sustained corticosteroids had similar baseline NTx levels to those who did not (223 ± 142 nmol BCE/mmol Cr vs 210 ± 190 nmol BCE/mmol Cr; p = 0.25). At follow-up, patients who received calcitriol alone (n = 44) had elevated NTx levels that were essentially unchanged from baseline (187 ± 146 nmol BCE/mmol Cr vs 178 ± 123 nmol BCE/mmol Cr; p = 0.59). In contrast, the patients who received both calcitriol and pamidronate (n = 11) had a significant decrease in urine NTx at follow-up (329 ± 238 nmol BCE/mmol Cr vs 100 ± 85 nmol BCE/mmol Cr; p < 0.01; Fig 1).

The four patients with metastatic cancer had significantly higher urine NTx levels at baseline than those patients without cancer (426 ± 391 nmol BCE/mmol Cr vs 197 ± 143 nmol BCE/mmol Cr; p = 0.01). Two of these patients were treated with calcitriol alone with little change in NTx levels (247 ± 210 nmol BCE/mmol Cr vs 203 ± 93 nmol BCE/mmol Cr). The other
two received both treatments, with NTx levels that decreased from 605 ± 535 to 122 ± 91 nmol BCE/mmol Cr.

**DISCUSSION**

CCI patients have accelerated bone breakdown that may lead to significant bone loss during the chronic critical illness.1 Following successful weaning and recuperation, bone losses may be difficult to replace, resulting in a lifelong increased risk for osteoporotic fractures. Identification and treatment of this metabolic bone disease accompanying chronic critical illness may prevent debilitating fractures that compromise overall quality of life after recovery. Theoretically, as CCI patients engage in physical therapy, resume weight bearing, and improve their overall nutritional and medical status, bone hyperresorption will abate and long-term treatment will not be necessary.

At baseline, our patients’ urine NTx levels averaged 215 ± 175 nmol BCE/mmol Cr. To provide a context, this level is four times that found in studies of postmenopausal women at risk for developing osteoporosis. Left untreated, a sustained urine NTx of 67 U has been shown to lead to a 17.3-times higher risk of significant bone mineral density loss at 1 year in postmenopausal women, as measured by dual energy x-ray absorptiometry.10

We had previously hypothesized that bone hyperresorption in CCI patients was caused by a combination of vitamin D deficiency and immobilization hyperresorption.1 CCI patients are at high risk for vitamin D deficiency secondary to the following: (1) decreased dietary vitamin D or malabsorption; (2) decreased sunlight exposure; (3) impaired hepatic 25-vitamin D formation; and/or (4) impaired renal 1,25-vitamin D formation. Vitamin D deficiency disinhibits PTH secretion either directly or indirectly via decreased GI calcium absorption, and leads to an
elevated serum PTH level. This secondary hyperparathyroidism causes increased bone resorption and release of NTx from bone that is then excreted into the urine in abnormally high amounts (Fig 2).1

If vitamin D deficiency is the primary cause of accelerated bone destruction, then vitamin D replacement with calcitriol (1,25-vitamin D) would be expected to lead to normalization of both serum PTH and urinary NTx levels. Although we found that treatment with calcitriol alone did significantly decrease serum PTH levels, suggesting correction of vitamin D deficiency, urine NTx levels remained unchanged. This suggests that correction of vitamin D deficiency and the secondary hyperparathyroidism it leads to is inadequate to stop the accelerated bone breakdown of CCI patients.

A significantly better biochemical response was seen in patients who were treated with both calcitriol and pamidronate. Bisphosphonates such as pamidronate impair bone resorption directly, by inhibiting the recruitment and function of osteoclasts and indirectly, by stimulating osteoblasts to produce an inhibitor of osteoclast formation, and by decreasing circulating levels of osteoclast stimulators, such as interleukin (IL)-6.11

Since these data support the notion that the accelerated destruction of bone in CCI patients is essentially independent of PTH, there must be other mechanisms to explain this phenomenon. One partial explanation might be prolonged bed rest. Stress, disease, and/or immobilization with prolonged bed rest stimulates the production of certain cytokines and local bone growth factors. These substances act to increase bone resorption and liberate calcium and NTx, which results in increased urinary calcium and NTx. In this setting, serum PTH is suppressed below the normal range due to the increased release of calcium from bone into the circulation. Low PTH levels suppress renal 1,25-vitamin D formation.

Our patients were hospitalized a median of > 3 weeks before RCU admission, with the majority of that time spent critically ill at bed rest in the ICU. Bone mineral homeostasis and matrix integrity changes that occur with immobilization have been studied in normal people, spinal cord injury patients, hemiplegic patients following stroke, and astronauts in weightless environments.13–15 Normal people kept at strict bed rest for 10 days have a marked rise in urine excretion of calcium and hydroxyproline that occurs by the fourth day, with a significant drop in serum 1,25-vitamin D levels. Even 6 weeks after remobilization, urine hydroxyproline excretion remains abnormally increased, consistent with continued breakdown of bone matrix.14 Prolonged immobilization in spinal cord injury has long been known to result in hypercalciuria, hypercalcemia, accelerated bone resorption, and osteoporosis.15,16

In addition to immobilization, we propose a broader theory: that the bone hyperresorption in
CCI patients involves activation of the immune-neuroendocrine axis. Van den Berghe et al. have shown that protracted critical illness leads to a specific pattern of neuroendocrine responses, including activation of the hypothalamic-pituitary-adrenal axis, central hypogonadism, low thyroxine and triiodothyronine syndrome, and suppressed growth hormone pulsatility with low serum insulin-like growth factor-1 levels. This results in sustained hypercortisolism and both male and female hypogonadism. In addition to these hormonal changes, we hypothesize that CCI patients have bi-directional interactions between their hypothalamic-pituitary-adrenal axis and their immune systems, leading to elevated levels of cytokines, such as IL-1 and IL-6, which affect bone metabolism. IL-6 in combination with IL-1 is a major inducer of osteoclast production and mediator of pathogenic bone resorption, and is released systemically in response to inflammatory and noninflammatory stress. This hormonal and cytokine milieu favors decreased bone formation and increased bone resorption, and may be the cause of accelerated bone destruction in CCI patients.

This retrospective study is limited by the small number of patients included, especially in the group treated with both calcitriol and pamidronate. In addition, this preliminary report, we report only our patient’s biochemical response to treatment without being able to show if this leads to any outcome benefit. The study of interventions intended to block accelerated bone destruction has three discrete steps: first, evaluation of the impact of therapies on biochemistry; second, evaluation of the impact of therapies on bone density; and third, long-term outcome studies that look at morbidity and mortality. The data shown herein support the need for a prospective, randomized trial to determine if a biochemical response to treatment of accelerated bone destruction while patients are CCI leads to differences in bone density and objective short- or long-term outcome benefits for these patients.

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