Reversal of Severe Osteoporosis With Vitamin B_{12} and Etidronate Therapy in a Patient With Pernicious Anemia

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Pernicious anemia has recently been recognized as a risk factor for osteoporosis and fractures. Although vitamin B_{12} is important for osteoblast function, the effect of vitamin B_{12} replacement in states of vitamin B_{12} deficiency on bone density and fracture incidence is not known. We report 2-year follow-up data from a patient with severe osteoporosis, multiple vertebral compression fractures, and pernicious anemia who exhibited a dramatic response to treatment with vitamin B_{12} and cyclic etidronate. Serial bone density measurements demonstrated a 15% and 17% increase in the lumbar and greater trochanter regions, respectively, and a 79% increase in the femoral neck region over the 2-year follow-up period. In addition to normalization of bone density compared with age-matched controls, no subsequent vertebral fractures were noted in the 2-year period following initiation of vitamin B_{12} and etidronate therapy. This case demonstrates that osteoporosis associated with pernicious anemia may be markedly improved by vitamin B_{12} replacement and cyclic etidronate therapy.

PERNICIOUS ANEMIA has been identified as a risk factor for osteoporosis[1] and proximal femur, distal forearm, and vertebral fractures.[2] Vitamin B_{12} is thought to be important for osteoblast activity, and treatment of pernicious anemia with vitamin B_{12} increases serum markers of bone formation.[3] However, the effect of vitamin B_{12} replacement on bone density and fracture rate over time in patients with pernicious anemia and osteoporosis has not been studied. Bisphosphonates administered in a cyclic regimen have been used with success to treat postmenopausal osteoporosis;[4,5] however, their efficacy in treating osteoporosis due to other causes is not known. Here we report data from a 2-year observation period of a man with pernicious anemia accompanied by severe osteoporosis and multiple vertebral fractures in whom marked improvement in bone density and reduction in fracture incidence occurred while undergoing treatment with vitamin B_{12} and cyclic etidronate.

CASE REPORT

A 68-year-old man presented with a 2-year history of multiple thoracic and lumbar vertebral compression fractures. He had initially sought medical attention for an episode of thoracic back pain. Evaluation by his local physician revealed compression fractures of the eighth and ninth thoracic vertebrae, with normal-appearing lumbar vertebrae. A subsequent episode of acute back pain revealed mild compression fractures of the first and second lumbar vertebrae. Salmon calcitonin therapy was initiated, but moderate compression fractures of both the fifth and eleventh thoracic vertebrae developed. Upon presentation to our clinic, he had been receiving subcutaneous salmon calcitonin 100 IU daily for the previous 7 months, as well as 1,666 mg elemental calcium and 667 IU vitamin D daily for 2 years.

Screening studies for etiologies of osteoporosis were performed. Serum electrolytes, calcium, phosphorus, alkaline phosphatase, folate, testosterone, thyroid-stimulating hormone, parathyroid hormone, and protein electrophoresis were normal. The hemoglobin level was 7.7 mmol/L (12.4 g/dL). The hematocrit value was 36.5% with a mean cell volume of 101 μm^3/cell. The red blood cell count was $3.5 \times 10^6/mm^3$, and the white blood cell count was $5,200/mm^3$. The serum vitamin B_{12} level was low at 116 pmol/L (157 pg/mL; normal > 200 pg/mL). Small-bowel mucosal biopsies were normal. A Schilling test was consistent with the diagnosis of pernicious anemia, ie, a first-phase excretion of 5.2% in 24 hours (normal > 8.0%) and a second-phase (with intrinsic factor) excretion of 13.1% in 24 hours. A parietal cell antibody titer was positive at a 1:20 dilution.

Bone density measurements obtained by dual-photon absorptiometry ([DPA] Lunar DP3, Madison, WI) confirmed the presence of osteopenia in the lumbar spine and proximal femur (Table 1). The lumbar spine density may have been overestimated due to the presence of compression fractures in this area.

Treatment was initiated with monthly intramuscular injections of vitamin B_{12}. In addition, a course of cyclic etidronate therapy consisting of 400 mg orally per day for the first 2 weeks of every 3 months was prescribed; 1,500 mg elemental calcium and 400 IU vitamin D were administered daily throughout the treatment period. No new episodes of back pain occurred. No subsequent vertebral compression fractures were noted on follow-up spine films at 2 years. The serum vitamin B_{12} level increased to 295 pmol/L (400 pg/mL). The anemia improved, and the mean cell volume decreased to 96 μm^3/cell.

Follow-up bone density measurements were obtained using dual-energy x-ray absorptiometry ([DEXA] Lunar DPX) after 2 years of treatment (Table 1). The bone density in both the lumbar spine and proximal femur had increased markedly and was normal for age.

DISCUSSION

There are no published reports describing the effect on bone disease of vitamin B_{12} replacement or other therapies in patients with osteoporosis due to pernicious anemia or other causes of vitamin B_{12} deficiency. This patient displayed a marked improvement in bone density with the combination of vitamin B_{12} and cyclic etidronate therapy.

The comparison of bone density measurements must be interpreted with an understanding of the different densitometry systems. A comparison of the two densitometry techniques used in this report (DPA and DEXA, Lunar) at both lumbar vertebrae and the femoral neck has shown a high

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Table 1. Bone Density Measurements Initially and Following 2 Years of Therapy With Vitamin B_{12} and Etidronate

	Initial*	2 Years†	% Change‡
Lumbar vertebrae 2-4			
Bone density (g/cm²)	1.097	1.254	+15
Compared with young normal (%)	87.0	101	
Compared with age-matched (%)	88.1	103	
Femoral neck			
Bone density (g/cm²)	.51	.912	+79
Compared with young normal (%)	50.7	88	
Compared with age-matched (%)	56.3	103	
Greater trochanter			
Bone density (g/cm²)	.64	.751	+17
Compared with young normal (%)	79.5	83	
Compared with age-matched (%)	79.7	89	

*Initial bone density measurements were performed using DPA (Lunar DP3 system).

†Two-year follow-up measurements were obtained using DEXA (Lunar DPX system).

‡DPX data were compared with DP3 data at L2-4 by applying the following equation: DPX = 1.072 DP3 − 0.095.[6]

correlation ($r > .97$).[6] In fact, the DEXA measurements tend to be slightly lower than the DPA measurements.[6] Taking this into account, the increase in bone density seen in this patient was more likely to have been underestimated rather than overestimated. Therefore, it is not possible to explain the improvement in bone density in this patient by differences in densitometry technique. Indeed, it is most likely that the therapy instituted in this patient was responsible for the dramatic improvement in bone density.

Since this patient received both vitamin B_{12} and cyclic etidronate, it is unclear whether a single agent or a combination of agents acting synergistically was responsible for the reversal of osteoporosis. Etidronate is thought to act primarily by decreasing bone resorption. Cyclic administration of etidronate has been associated with modest increases in bone density in patients with postmenopausal osteoporosis.[4,5] Dramatic increases in bone mineral density, as seen in this patient, have not been reported as a result of etidronate therapy alone. Vitamin B_{12} appears to be important for osteoblast activity and bone formation.[3] Whether vitamin B_{12} alone could be responsible for the improvement seen in this patient is unknown. Theoretically, by administering these two agents simultaneously, the rate of bone resorption would be decreased by etidronate while at the same time vitamin B_{12} replacement would allow bone formation to proceed, resulting in a net increase in bone density above what might be expected from vitamin B_{12} alone.

The dramatic improvement seen in this patient suggests that osteoporosis due to vitamin B_{12} deficiency may be reversible and easily treated. Vitamin B_{12} deficiency is a common (and commonly unrecognized) disorder, with a prevalence of up to 10% in the elderly population.[7] Vitamin B_{12} deficiency often accompanies atrophic gastritis, and the prevalence of atrophic gastritis in the elderly population is approximately 30%.[8] Vitamin B_{12} deficiency may also play a role in the osteoporosis that commonly develops following gastrectomy and gastric bypass procedures.[9,10] Whether treatment with vitamin B_{12} replacement, either alone or in combination with cyclic etidronate, will be as effective a treatment for osteoporosis in other patients with vitamin B_{12} deficiency is a question that warrants investigation.

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