Chapter 23
Osteomalacia: A Cause of Bisphosphonate Failure

Michael Pazianas and Mone Zaidi

Objectives

1. To understand presentations of vitamin D deficiency
2. To understand how vitamin D deficiency can confound interpretation of dual-energy x-ray absorptiometry (DXA; bone densitometry) results, particularly following bisphosphonate therapy.

Case Presentation

A 52-year-old woman from India who moved to Minnesota 6 years ago was referred to us because of a clinically significant decline in her bone mineral density (BMD) despite treatment with bisphosphonates. She also complained of back pain and muscular weakness.

Upon entering perimenopause, she visited her family physician for a comprehensive osteoporosis risk assessment. Her menses were delayed at age 16, but were regular since then. She had never been pregnant. There was no other significant medical history, and she was not on medications that would increase the risk of osteoporosis. Risk factors, including her family history, were negative for osteoporosis. Her weight at 140 lb (63.5 kg) and height at 5’5” (1.68 m) had been stable. Clinical examination was unremarkable.

Her family doctor requested a DXA, which showed a low T-score for both lumbar spine (L1–L4) and total hip at –2.2 and –2.3, respectively. Routine blood work showed normal serum creatinine and total calcium at 8.9 mg/dL (normal range 8.5–10.5 mg/dL). Serum 25-OH-vitamin D was 10 ng/mL (normal sufficient: >32 ng/mL).

The patient was started on an aminobisphosphonate, which she took “religiously” every week. One year later, a repeat DXA scan performed on the same densitometer
How the Diagnosis Was Made

Two clinical issues arose. The first was that of her low density at the outset, the question being whether she had lost bone or failed to acquire it, as is commonplace. The second issue centered on the further decline in her BMD following a potent bisphosphonate.

The Study of Women’s health Across the Nation (SWAN) has shown that women could lose bone at the highest rate around late perimenopause, even in the absence of an ovarian shut down [1]. However, it is likely that this patient’s low BMD at the outset resulted from not having achieved peak bone mass due to late onset of her menses, on the second issue, measurement of a bone resorption marker, such as urinary N-telopeptide, would have provided vital information. A high, >38 nmol/mmol Cr would have indicated ongoing bone loss, and a low level would have provided the assurance that the patient had not entered into the rapid perimenopausal bone loss phase. In the latter case, it is suggested that a DXA be repeated a year later, and that the patient be informed that she will be disadvantaged compared with her peers upon entering the phase of maximum bone loss. Hence, extreme caution is warranted.

That the BMD had declined at both sites, despite the patient’s being on a bisphosphonate, raises another level of concern. The question always is whether a secondary diagnosis is missed, or whether the patient is a true bisphosphonate failure. In such instances, it is critical to first exclude the possibility of artifacts, such as results from uncalibrated bone densitometers and inappropriately analyzed DXA scans. In follow-up measurements, a densitometer from a different manufacturer could produce widely discrepant results; this was not the case here, as the same technician performed the tests one year apart on the same densitometer. Precision error of the given DXA machine, generally below 3% and 5% at the vertebral column and hip, respectively, must be taken into consideration to label a change as being clinically significant. This percent change should be calculated from raw numbers (g/cm²) rather than from T-scores, as T scores are database-derived. This patient did have a significant decline at the lumbar spine and hip.

Almost 90% of cases of bone loss despite bisphosphonate therapy, in our experience, arise for reasons that are not truly medical. These include poor adherence (taking the medication irregularly) and poor compliance (taking the medication incorrectly). In the case of our patient, we believe that she was taking the medication every week, and separating it from meals and calcium pills by several hours.

The obvious cause of this falling BMD was her severe vitamin D deficiency, obvious from a serum 25-OH-vitamin D value of 10 ng/mL. Hence, upon referral, the patient should be worked up for causes other than osteoporosis, with osteomalacia the most likely diagnosis. Total serum calcium at 8.8 mg/dL and phosphorus at