fracture over a 5- or 10-year period. Treatment threshold depends on cost-effectiveness analyses but probably is ~1% per year of risk in the United States.

APPROACH TO THE PATIENT: Osteoporosis

The perimenopausal transition is a good opportunity to initiate a discussion about risk factors for osteoporosis and consideration of indications for a BMD test. A careful history and physical examination should be performed to identify risk factors for osteoporosis. A low Z-score increases the suspicion of a secondary disease. Height loss >2.5–3.8 cm (>1–1.5 in.) is an indication for VFA by DXA or radiography to rule out asymptomatic vertebral fractures, as is the presence of significant kyphosis or back pain, particularly if it began after menopause. In appropriate individuals, screening BMD and screening vertebral imaging should be recommended as above, even in the absence of any specific risk factors (Table 425-3). For patients who present with fractures, it is important to ensure that the fractures are not caused by an underlying malignancy. Usually this is clear on routine radiography, but on occasion, CT, MRI, or radionuclide scans may be necessary.

ROUTINE LABORATORY EVALUATION

There is no established algorithm for the evaluation of women who present with osteoporosis. A general evaluation that includes complete blood count, serum and 24-h urine calcium, renal and hepatic function tests, and a 25(OH)D level is useful for identifying selected secondary causes of low bone mass, particularly for women with fractures or very low Z-scores. An elevated serum calcium level suggests hyperparathyroidism or malignancy, whereas a reduced serum calcium level may reflect malnutrition and osteomalacia. In the presence of hypercalcemia, a serum PTH level differentiates between hyperparathyroidism (PTH↑) and malignancy (PTH↓), and a high PTHrP level can help document the presence of humoral hypercalcemia of malignancy (Chap. 424). A low urine calcium (<50 mg/24 h) suggests osteomalacia, malnutrition, or malabsorption; a high urine calcium (>300 mg/24 h) is indicative of hypercalciuria and must be investigated further. Hypercalciuria occurs primarily in three situations: (1) a renal calcium leak, which is more common in males with osteoporosis; (2) absorptive hypercalciuria, which can be idiopathic or associated with increased $1,25(OH)_2D$ in granulomatous disease; or (3) hematologic malignancies or conditions associated with excessive bone turnover such as Paget's disease, hyperparathyroidism, and hyperthyroidism. Renal hypercalciuria is treated with thiazide diuretics, which lower urine calcium and help improve calcium economy.

Individuals who have osteoporosis-related fractures or bone density in the osteoporotic range should have a measurement of serum 25(OH)D level, because the intake of vitamin D required to achieve a target level >20–30 ng/mL is highly variable. Vitamin D levels should be optimized in all individuals being treated for osteoporosis. Hyperthyroidism should be evaluated by measuring thyroid-stimulating hormone (TSH).

When there is clinical suspicion of Cushing's syndrome, urinary free cortisol levels or a fasting serum cortisol should be measured after overnight dexamethasone. When bowel disease, malabsorption, or malnutrition is suspected, serum albumin, cholesterol, and a complete blood count should be checked. Asymptomatic malabsorption may be heralded by anemia (macrocytic—vitamin B_{12} or folate deficiency; microcytic—iron deficiency) or low serum cholesterol or urinary calcium levels. If these or other features suggest malabsorption, further evaluation is required. Asymptomatic celiac disease with selective malabsorption is being found with increasing frequency; the diagnosis can be made by testing for antigliadin, antiendomysial, or transglutaminase antibodies but may require endoscopic biopsy. A trial of a gluten-free diet can be confirmatory (Chap. 349). When osteoporosis is found associated with symptoms of rash, multiple allergies, diarrhea, or flushing, mastocytosis should be excluded by using 24-h urine histamine collection or serum tryptase.

Myeloma can masquerade as generalized osteoporosis, although it more commonly presents with bone pain and characteristic "punched-out" lesions on radiography. Serum and urine electrophoresis and or serum free light chains are required to exclude this diagnosis. More commonly, a monoclonal gammopathy of unclear significance (MGUS) is found, and the patient is subsequently monitored to ensure that this is not an incipient myeloma. Approximately 1% of patients with MGUS progress to myeloma each year. A bone marrow biopsy may be required to rule out myeloma (in patients with equivocal electrophoretic results) and also can be used to exclude mastocytosis, leukemia, and other marrow infiltrative disorders such as Gaucher's disease. MGUS syndromes, although benign, may also be associated with reduced bone mass and elevated bone turnover.

BONE BIOPSY

Tetracycline labeling of the skeleton allows determination of the rate of remodeling as well as evaluation for other metabolic bone diseases. The current use of BMD tests, in combination with hormonal evaluation and biochemical markers of bone remodeling, has largely replaced the clinical use of bone biopsy, although it remains an important tool in clinical research and assessment of mechanism of action of medication for osteoporosis.

BIOCHEMICAL MARKERS

Several biochemical tests are available that provide an index of the overall rate of bone remodeling (Table 425-4). Biochemical markers usually are characterized as those related primarily to *bone formation* or *bone resorption*. These tests measure the overall state of bone remodeling at a single point in time. Clinical use of these tests has been hampered by biologic variability (in part related to circadian rhythm) as well as analytic variability, although the latter is improving.

TABLE 425-3 INDICATIONS FOR VERTEBRAL IMAGING

Consider vertebral imaging tests in the following individuals:

- In all women age 70 and older and all men age 80 and older if bone mineral density (BMD) T-score is –1.0 or below
- In women age 65–69 and men age 75–79 if BMD T-score is –1.5 or below
- In postmenopausal women age 50–64 and men age 50–69 with specific risk factors:
  - Low-trauma fracture
  - Historical height loss of 1.5 in. or more (4 cm)
  - Prospective height loss of 0.8 in. or more (2 cm)
  - Recent or ongoing long-term glucocorticoid treatment

Source: From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

TABLE 425-4 INDICATIONS FOR BIOCHEMICAL MARKERS

Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density.
- Predict extent of fracture risk reduction when repeated after 3–6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Predict rapidity of bone loss.
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy.
- Help determine duration of "drug holiday" (data are quite limited to support this use, but studies are under way).

Abbreviations: BMD, bone mineral density; FDA, U.S. Food and Drug Administration.

Source: Adapted from the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.