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# Evaluating Patients for Secondary Causes of Osteoporosis

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## Abstract

**Purpose of Review** This review provides suggestions for the evaluation of patients with osteoporosis in order to assure that the diagnosis is correct, to identify potentially correctable conditions contributing to skeletal fragility and fracture risk, and to assist in individualizing management decisions.

**Recent Findings** Some patients who appear to have osteoporosis have another skeletal disease, such as osteomalacia, that requires further evaluation and treatment that is different than for osteoporosis. Many patients with osteoporosis have contributing factors (e.g., vitamin D deficiency, high fall risk) that should be addressed before and after starting treatment to assure that treatment is effective and safe. Evaluation includes a focused medical history, skeletal-related physical examination, assessment of falls risk, appropriate laboratory tests, and rarely transiliac double-tetracycline labeled bone biopsy.

**Summary** Evaluation of patients with osteoporosis before starting treatment is essential for optimizing clinical outcomes.

**Keywords** Osteoporosis · Osteomalacia · Risk · Testing · Laboratory

## Introduction

Osteoporosis is diagnosed when bone mineral density (BMD) T-score is ≤ −2.5 at the lumbar spine, femoral neck, total proximal femur, or 33% (one-third) radius in appropriately selected patients using dual-energy X-ray absorptiometry (DXA) or another validated technology [1, 2••]. Some guidelines recommend diagnosing osteoporosis in patients with certain types of prior fracture regardless of T-score [3] or when fracture probability estimated by a fracture risk algorithm, such as FRAX [4], exceeds country-specific treatment thresholds [5••]. Regardless of how osteoporosis is diagnosed, the diagnosis is presumptive until other disorders that masquerade as osteoporosis (e.g., osteomalacia) have been considered and excluded. Patients with osteoporosis may have factors other than advancing age or estrogen deficiency that contribute to skeletal fragility. Collectively called secondary causes of osteoporosis, these are medical conditions, diseases, and medications [6] that cause bone loss or failure to attain optimal peak bone mass. Secondary causes of osteoporosis are common. One review of the literature found that secondary causes of osteoporosis were identified in about two-thirds of men, one-half of pre- and perimenopausal women, and one-fifth of postmenopausal women with osteoporosis [7]. In a cross-sectional study of 664 women with newly diagnosed peri- and postmenopausal osteoporosis referred to an osteoporosis specialty center, more than one-half had a history of taking medications or having diseases known to have adverse skeletal effects [8, 9]. Of the remaining women with no known contributors to osteoporosis, 173 had a complete battery of laboratory tests. It was found that 4 simple cost-effective tests (serum calcium, serum intact parathyroid hormone [PTH], 24-h urinary calcium, and thyrotropin for patients on thyroid replacement therapy) identified over 85% of those with a previously unrecognized disorder of bone and mineral metabolism. The reported rates of abnormal tests vary according to factors that include the practice setting, the population studied, tests selected, and definitions for abnormal tests [7, 10–12]. This is a review and update of strategies to identify secondary causes of osteoporosis, with the ultimate goal of correcting those that are correctable in order to optimize the effectiveness and safety of interventions to reduce fracture risk.

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## Is It Really Osteoporosis?

Skeletal diseases other than osteoporosis may result in low BMD and fractures. As examples, T-score ≤ −2.5 can be due to osteomalacia, osteogenesis imperfecta, chronic kidney disease-mineral and bone disorder (CKD-MBD), and other disorders, any of which might occur independently of osteoporosis or concomitantly with osteoporosis [13••]. Localized non-osteoporosis bone diseases, such as avascular necrosis, Paget's disease of bone, or skeletal malignancy, can cause low-trauma fractures. Treating such patients for osteoporosis may delay necessary treatment for the underlying problem and could in some situations be harmful, as when a potent antiresorptive drug is given to a patient with unrecognized hypophosphatasia, which might increase the risk of an atypical femur fracture [14, 15]. The correct non-osteoporosis diagnosis can usually be made by medical history, physical examination, laboratory testing, and/or imaging. The same process is used to identify conditions contributing to the development of osteoporosis [16–18].

## Medical History

A focused medical history can reveal important information about factors contributing to the development of osteoporosis and fracture risk, as well as the presence of other disorders associated with skeletal fragility. This includes history of childhood and adolescent events of interest ranging from blue sclerae at birth (possibly due to osteogenesis imperfecta) to early loss to deciduous teeth (a manifestation of infantile/childhood hypophosphatasia) to delayed puberty (a risk factor for low peak bone mass). For women, the age of menarche, age of menopause, number of pregnancies, and lactation history should be ascertained. Personal and family history of fractures should be ascertained. Lifestyle issues, such as nutrition, physical activity, occupation, recreational activities, sun exposure, home environment, drugs, nutritional supplements, and the use of assistive devices for ambulation, are important in assessing fracture risk and making treatment recommendations. Age is an independent risk factor for fracture and a consideration for measuring BMD with many clinical practice guidelines [2, 5, 19, 20]. Patient questionnaires, such as the Stopping Elderly Accidents, Deaths and Injuries (STEADI) screening algorithm [21], can be used to assess fall risk and the need for interventions to prevent falls. Table 1 provides examples of helpful historical information and implications for patient care.

Effective use of FRAX [4] for estimating the 10-year probability of fracture is dependent on obtaining correct historical information for input of FRAX-related clinical risk factors: previous fracture, parent with hip fracture, current tobacco smoker, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis (when femoral neck BMD is not available), and alcohol 3 or more units per day. Incorrect information for one or more of these can influence the results and possibly alter treatment decisions. It is prudent to verify information that is provided by patients; as examples, it is common for patients to believe they have rheumatoid arthritis (a risk factor) when it is really osteoarthritis (not a risk factor) or to count a broken toe as a previous fracture when it should not be included as a risk factor for FRAX. Since FRAX may under- or overestimate fracture risk in a quantifiable way in a variety of clinical circumstances, adjustments to the initial FRAX algorithm may be considered according to the dose of glucocorticoids [22], the recency of previous fractures [23], the age of parental hip fracture [24], type 2 diabetes mellitus [25], spine-hip T-score discordance [26], and trabecular bone score [27].

## Physical Examination

Findings on physical exam (Figure 1) may provide clues for factors contributing to poor skeletal health, recognize patients at high risk of falls, and identify consequences of prior fractures.

### Vital Signs

Measuring height accurately with a wall-mounted stadiometer and comparing it with historical maximum height is used to determine historical height loss (HHL). When HLL is > 4.0 cm (1.5 inches) and T-score is < −1.0, lateral spine imaging by DXA or conventional radiography should be considered [2]. A finding of a previously unrecognized vertebral fracture may change estimation of fracture risk, diagnostic classification, and treatment decisions [2]. There is an association between lower body mass index (BMI) and higher risk of all osteoporotic fractures, with variable magnitude of risk depending on fracture site and attenuation of the association when adjusted for BMD [28]. Obesity appears to reduce fracture risk at most, but perhaps not all skeletal sites, with frailty attenuating the protective effect of obesity for major osteoporotic fractures [29]. A high pulse rate could be a sign of hyperthyroidism and a high respiratory rate could be a sign of chronic obstructive pulmonary disease (COPD), both risk factors for osteoporosis and fractures [30, 31].

### Ambulation, Strength, and Balance

Observing the patient coming in and out of an examination room, getting in and out of a chair, and getting on and off an examination table can provide important information about strength and balance. Causes of impaired ambulation include neurological diseases (e.g., stroke, multiple sclerosis), arthritis, muscle weakness, and vestibular disturbances. Simple

**Table 1** Historical information for the assessment of patients with osteoporosis. These are selected examples of information that can be obtained from a focused medical history and examples of implications for skeletal health. This is not a complete list. Additional historical information may be helpful depending on clinical circumstances

| Example | Implications |
|---|---|
| Back pain | Unexplained back pain in a patient with osteoporosis, especially with historical loss of height, suggests possible vertebral fracture(s) |
| Family history of fractures | Parental hip fracture is a risk factor for FRAX |
| Prior fractures | Fragility fractures in childhood suggest an inherited skeletal disorder. Adult fractures, including traumatic fractures in older adults, are a risk factor for future fractures |
| Early tooth loss | Loss of deciduous teeth before age 5 years may occur in patients with hypophosphatasia. Dentinogenesis imperfecta may occur in patients with osteogenesis imperfecta. |
| Hearing loss | This may occur with osteogenesis imperfecta and in some patients with Paget's disease of bone |
| Unhealthy lifestyle (smoking, excess alcohol, lack of physical activity) | These are modifiable risk factors for fracture |
| Falls | Prior falls is a risk factor for fall-related injuries, including fractures |
| Surgery | Bariatric surgery, gastrectomy, or bowel resection may result in malabsorption of essential skeletal nutrients. Thyroidectomy or parathyroidectomy may increase the risk of hypocalcemia with antiresorptive therapy. Organ transplantation and its treatment increase fracture risk. Bilateral oophorectomy in a premenopausal woman is a cause of early menopause |
| Medications | Medications known to be harmful to bones, such as glucocorticoids and aromatase inhibitors, should be identified. Past experiences and preferences with medications to treat osteoporosis should be discussed |
| Nutritional supplements | Some supplements, such as biotin, may interfere with some laboratory assays. Excessive amounts are calcium or vitamin D may be harmful |
| Gastrointestinal disorders | Celiac disease, inflammatory bowel disease, or chronic liver disease can cause malabsorption of essential skeletal nutrients. An esophageal stricture or dysphagia is a contraindication for oral bisphosphonate therapy |
| Thromboembolic disorders | Estrogen and raloxifene should be avoided in patients at high risk for blood clots |
| Cardiovascular disease | The product label for romosozumab warns that it may increase the risk of myocardial infarction, stroke and cardiovascular death |
| Chronic pulmonary disease | These patients have increased risk of fracture and vulnerability to further reduction of pulmonary function with vertebral fractures |
| Chronic kidney disease | This may cause renal osteodystrophy and have implications for the type of treatment that is selected. |
| Radiation therapy to the skeleton | This is a warning and precaution regarding treatment with teriparatide and abaloparatide |
| Joint pain and swelling | Chronic inflammatory diseases, such as rheumatoid arthritis, are risk factors for osteoporosis |
| Bone pain and weakness | Osteomalacia should be considered |

office-based balance tests include one-leg standing and tandem gait testing. Quantitative tests to assess fall risk include the Timed Up and Go (TUG) test [32], 30-second Sit-To-Stand (30STS) [33], and 5 Times Sit-To-Stand (5TSTS) test [34]. TUG time is the time to rise from the edge of standard chair, walk 10 m, and return to sitting in the chair. The 30STS test records the number of times standing from a seated position in 30 s. With 5TSTS, the patient begins sitting against the back of the chair with arms folded across the chest, with time to fully stand and sit for 5 times measured. TUG or 5TSTS time ≥ 12 s has been associated with increased risk of falls in community-dwelling older adults [35]. Fewer than 7 repetitions in a modified 30STS test was associated with increased risk of falls in a study of elderly institutionalized adults [36]. Patients at high risk for falls should be considered for interventions to reduce the risk.

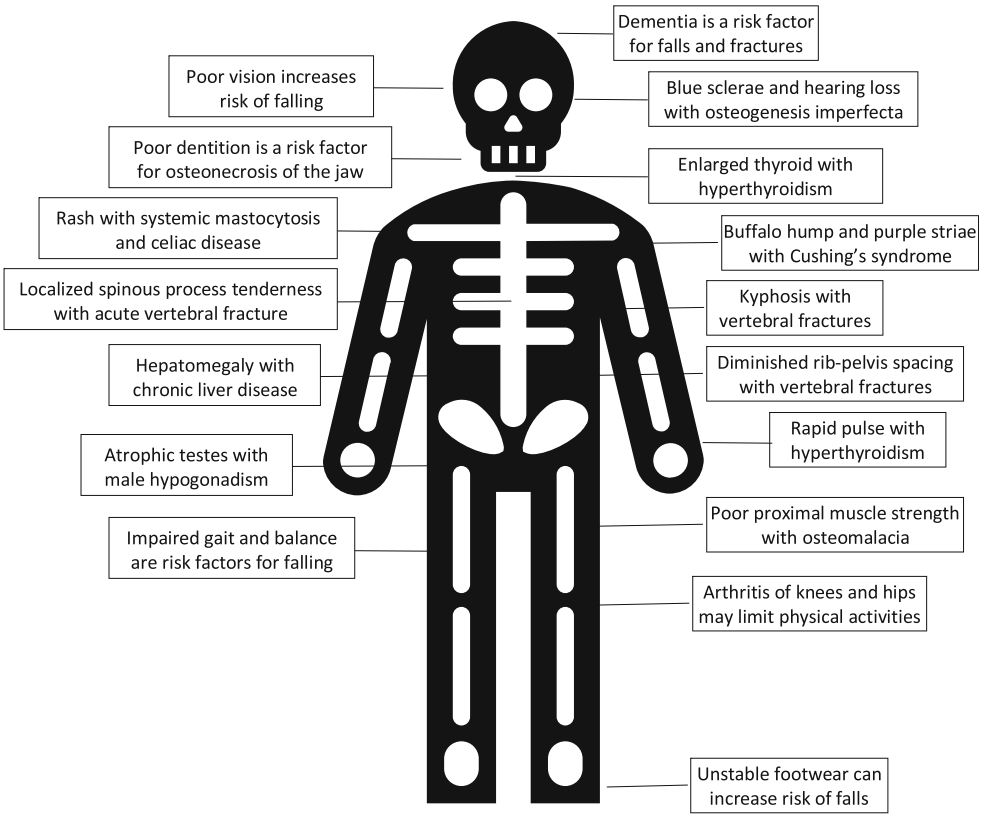


**Figure 1** Physical examination of patients with osteoporosis. Physical abnormalities may suggest the presence of skeletal disorders other than osteoporosis, show deformities due to previous fractures, and identify risk factors for falls. These are examples of findings that may influence the management of patients with osteoporosis

## Skin, Joints, and Skeleton

A skin rash could be related to a disease of skeletal importance, such as systemic mastocytosis, or could be an adverse reaction to drug therapy for osteoporosis. Surgical scars may represent procedures of skeletal relevance, such as thyroidectomy or parathyroidectomy, that the patient failed to mention. Examination of the joints may reveal findings of rheumatoid arthritis, a risk factor for fracture. Skeletal deformities may be the result of prior fractures, as with kyphosis caused by vertebral fractures. Localized spinous process tenderness may be the result of an acute vertebral fracture at that level. Some skeletal deformities may impair ambulation and increase risk of falls.

## Head, Eyes, Ears, and Throat

Blue sclerae are suggestive of osteogenesis imperfecta. Poor dentition may be seen with osteogenesis imperfecta or hypophosphatasia and is a risk factor for osteonecrosis of the jaw, as is a finding of mandibular tori. Thyromegaly may be present in patients with thyrotoxicosis, a risk factor for osteoporosis.

## Cardiovascular and Pulmonary

Physical findings of congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD) are suggestive of frailty and increased risk of falls. Treatment of these diseases with drugs such as diuretics and glucocorticoids may have implications regarding calcium homeostasis and fracture risk. Vertebral fractures in a patient with COPD are a special concern, as this may worsen pulmonary function that is already compromised. Thromboembolic events may occur with some medications used to treat osteoporosis, such as estrogen and raloxifene. There is a potential increase in the risk of cardiovascular events with romosozumab that should be taken into consideration before prescribing this medication.

## Gastrointestinal

Hepatomegaly may be a sign of chronic liver disease, a risk factor for fracture. Abdominal protuberance and reduced rib-pelvis space can be the result of vertebral fractures. An abdominal surgical scar may be the result of a bowel resection or bariatric surgery that could cause malabsorption and osteoporosis.

## Laboratory Tests

Every patient with osteoporosis can benefit from basic laboratory tests before starting treatment and some may need more extensive testing, depending on clinical circumstances. The results of these tests may influence patient management decisions by identifying conditions contributing to skeletal fragility requiring interventions instead of or in addition to those for osteoporosis. Some findings may be relevant in the selection of initial drug therapy. Recommendations for testing have been provided by organizations that include the American Association of Clinical Endocrinologists [5], the National Osteoporosis Foundation [19], Osteoporosis Canada [37], and the UK National Osteoporosis Guideline Group (NOGG) [38]. The following is a composite of published recommendations, summarized in Table 2 with a rationale for performing each of them. A focused medical history, physical examination, and appropriate testing will identify factors contributing to low BMD and fractures in most patients (Table 3) and guide treatment decisions.

### Laboratory Testing for All Patients with Osteoporosis

Laboratory tests that are commonly recommended for all patients are blood chemistries (e.g., calcium, albumin, phosphorus, alkaline phosphatase, creatinine), serum 25-hydroxyvitamin D (25-OH-D), 24-h urine for calcium, and a complete blood count.

### Calcium

Abnormal serum calcium should be evaluated and treated before treatment is started. Treatment with an antiresorptive agent may cause or exacerbate pre-existing hypocalcemia [39, 40]. Treatment may be less than fully effective in a patient with baseline hypocalcemia; normocalcemia is requirement for participation in clinical trials of compounds for the treatment of osteoporosis. Patients with a high baseline calcium level could have primary hyperparathyroidism and need surgical treatment [41]. Total serum calcium is probably an adequate screening test for most patients, although calculation of albumin-adjusted calcium may be a better test, especially in patients with extremes of serum albumin. A commonly used adjustment formula in SI units for a patient with low serum albumin is to correct the total serum calcium by adding 0.2 mmol/L for every 1.0 g/L the albumin is < 40 g/L; conversely, for patients with high serum albumin, to correct the total serum calcium by subtracting 0.2 mml/L for every 1.0 g/L the albumin is > 40 g/L. The equivalent in conventional units for a patient with low serum albumin is to correct the total serum calcium by adding 0.8 mg/dL for every 1.0 g/dL the albumin is < 4.0 g/dL, and for patients with high serum albumin, to correct the total serum calcium by subtracting 0.8 mg/dL for every 1.0 g/dL the albumin is > 4.0 g/dL. Several equations are available for the calculation [42–45], with uncertainty regarding which is best for use in clinical practice [46] and lack of consensus on whether the corrections are equally valid in patients with low and high serum albumin. Serum ionized calcium level generally remains stable despite fluctuations of albumin levels [47]; its measurement may be a useful alternative to total or albumin-adjusted serum calcium when the true calcium status is uncertain [46]. Normal serum ionized calcium is one of the criteria for diagnosing normocalcemic primary hyperparathyroidism [41]. Serum ionized calcium may be especially useful in the assessment of calcium homeostasis in patient with chronic kidney disease on dialysis [48].

### Phosphorus

Serum phosphorus is suggested in the initial evaluation because some patients who appear to have osteoporosis may have a hypophosphatemic disorder, such as tumor-induced osteomalacia [49] or hypophosphatemia associated with tenofovir [50], that requires different treatment than for osteoporosis.

### Alkaline Phosphatase

Measurement of serum alkaline phosphatase is helpful in identifying non-osteoporosis conditions, as with a high value in a patient in patients with Paget's disease of bone [51] or osteomalacia due to vitamin D deficiency [52] and low value in patients with hypophosphatasia [53].

### Creatinine

Serum creatinine, often with calculation of glomerular filtration rate (GFR), is routinely measured for multiple reasons. Chronic kidney disease (CKD) is associated with CKD-mineral and bone disorder (CKD-MBD) and renal osteodystrophy, with patients having bone turnover ranging from low (e.g., adynamic bone disease, osteomalacia) to high (e.g., osteitis fibrosa due to secondary hyperparathyroidism, mixed uremic osteodystrophy) associated with decreasing BMD, high fracture risk, and bone mineralization that may be normal or abnormal [54, 55]. There are therapeutic implications for management of skeletal health with each of these types of renal osteodystrophy. Some of the drugs used to treat patients with CKD or renal transplantation, such a glucocorticoids and immune suppressants, have adverse skeletal effects. Bisphosphonates are not recommended when renal function is very low (glomerular filtration rate [GFR] < 30–35 mL/min), although the balance of benefits and risks of bisphosphonates in CKD patients is not well established [56]. Two intravenous bisphosphonates, zoledronic acid and pamidronate, have been associated with acute renal toxicity that can largely be avoided by measures such as adjustment of the dose and/or rate of infusion and avoidance in high risk patients [57]. In a large study of postmenopausal women with osteoporosis treated with 3 annual doses

**Table 2** Clinically useful tests for the assessment of patients with osteoporosis. These tests can identify diseases and disorders other than osteoporosis that may need to be addressed before starting treatment. Test results may be helpful in selecting initial therapy to reduce fracture risk. The choice of tests should be individualized and in part depends on patient preference, availability, and cost

| Test | Rationale |
|---|---|
| Consider for all patients | |
| Serum calcium | High with primary hyperparathyroidism, low level should be corrected before treatment |
| Albumin | Calculation of albumin-adjusted calcium, assessment of nutritional status |
| Serum phosphorus | Hypophosphatemia is a cause of osteomalacia |
| Alkaline phosphatase | Low with hypophosphatasia, high with osteomalacia and Paget's disease of bone |
| Creatinine | Severe chronic kidney disease; glomerular filtration rate (GFR) often calculated |
| Vitamin D | Measure 25-hydroxyvitamin D and correct deficiency before starting treatment |
| 24-h urine calcium | Low value suggests malabsorption; high value may be hyperparathyroidism or idiopathic |
| Complete blood count | Abnormalities may be due to myeloma, malabsorption, or hematological malignancy |
| For some patients | |
| Liver enzymes | Elevated with chronic liver disease |
| Serum electrolytes | Hyponatremia is associated with osteoporosis; low bicarbonate with renal tubular acidosis |
| Serum iron | Low level in absence of bleeding may be due to malabsorption |
| Bone specific ALP | Potentially useful in evaluating patients with high total serum alkaline phosphatase (ALP) |
| Sedimentation rate | Erythrocyte sedimentation rate (ESR) may be high with myeloma, rheumatoid arthritis, etc. |
| Bone turnover marker | Independent risk factor for bone loss and fracture; may be useful to monitor therapy |
| Protein electrophoresis | An M-component on serum protein electrophoresis may be due to MGUS or myeloma |
| Ionized serum calcium | May be helpful when value for albumin-adjusted calcium is borderline abnormal |
| Thyrotropin | A low level may be seen with hyperthyroidism |
| Parathyroid hormone | Primary hyperparathyroidism can cause bone loss and fractures |
| Cortisol | For patients suspected of having Cushing's syndrome |
| Celiac antibodies | Celiac disease can cause osteoporosis due to malabsorption |
| Tryptase | High serum tryptase or urinary N-methylhistamine with systemic mastocytosis |
| Vitamin B6 | Often elevated with hypophosphatasia |
| Testosterone | Most useful in young men with unexplained osteoporosis |
| Skeletal imaging | X-ray, computed tomography, magnetic resonance imaging, radionuclide imaging, etc. |
| Genetic testing | May be helpful when inherited disorders are suspected |
| Small bowel biopsy | Abnormal findings with untreated celiac disease |
| Skin biopsy | Sometimes helpful in the diagnosis of osteogenesis imperfecta or systemic mastocytosis |
| Transiliac bone biopsy | Potentially for classifying renal osteodystrophy |

of zoledronic acid, transient changes in renal function were seen, although long-term renal function in these patients was no different than controls [58].

## Vitamin D

To assess vitamin D sufficiency in patients with osteoporosis, measurement of serum 25-OH-D (not 1,25-dihydroxyvitamin

**Table 3** Secondary causes of low bone density and fractures. These are examples of diseases and disorders that may contribute to the development of osteoporosis or conditions that can mimic osteoporosis. This is not intended to be all inclusive. Since the likelihood of encountering a patient with any one of these depends on the practice setting, the categories of common, uncommon, and rare are partly arbitrary

| Common | Uncommon | Rare |
|---|---|---|
| Low calcium intake | Myeloma | Cushing's syndrome |
| Vitamin D deficiency | Rheumatoid arthritis | Hypophosphatasia |
| Excessive alcohol | Organ transplantation | Systemic mastocytosis |
| Cigarette smoking | Hyperparathyroidism | Renal tubular acidosis |
| Excessive thyroid intake | Immobilization | Hemochromatosis |
| Malabsorption | Chronic liver disease | Turner's syndrome |
| Glucocorticoids | Gastrectomy | Hyperprolactinemia |
| Aromatase inhibitors | Eating disorders | Tumor-induced osteomalacia |
| Androgen deprivation therapy | Excess aluminum intake | Osteogenesis imperfecta |

D) is recommended [59]. The prevalence of vitamin D inadequacy is high and varies according to factors that include how it is defined, the assay used, skin pigmentation, geographic location, and lifestyle [60]. Very low vitamin D levels (e.g., < 25 nmol/L, < 10 ng/mL) can cause rickets in children and osteomalacia in adults [52]. Osteomalacia may be more common than previously recognized. Iliac crest biopsies were performed in association with autopsies of 401 men (mean age 59 years) and 274 women (mean age 68 years) who recently died due to circumstances such as motor vehicle or train accidents, assaults, suicides, and other unnatural or unexpected causes, with none having diseases or disorders known to have adverse skeletal effects [61]. Histomorphometric evidence of osteomalacia, conservatively defined as osteoid volume per bone volume (OV/BV) > 2%, was found in 26% of biopsy specimens. Blood samples taken at the time of autopsies showed no evidence of osteomalacia in subjects with serum 25-OH-D levels > 75 nmol/L (> 30 ng/mL), providing support for clinical recommendations using this value as a target for patients with osteoporosis. The study could not determine a minimum level of serum 25-OH-D below which osteomalacia was inevitable. Severe vitamin D deficiency should be corrected before starting a potent antiresorptive agent to avoid hypocalcemia with treatment [40], optimize treatment effect [62], and reduce the risk of an acute phase reaction with zoledronic acid [63].

## Urinary Calcium

Measurement of urine calcium is a common inexpensive test to assess disorders of calcium metabolism. Calcium excretion is usually measured in a 24-h urine collection, often with urine sodium (high sodium intake increases urinary calcium and risk of kidney stones [64]), urine creatinine, and total volume (normal creatinine and urine volume > 800 mL suggest that the collection is complete). It is standard for some laboratories to use an acid preservative during the collection or after it is submitted to the lab and some evidence that this may prevent the precipitation of urine minerals [65], although several studies have shown no significant difference in urinary calcium with or without acidification [66, 67]. Hypo- and hypercalciuria may be associated with adverse skeletal effects. Low urinary calcium in the setting of an adequate calcium intake and normal renal function suggests calcium malabsorption that may occur with conditions and disorders such as bariatric surgery [68], celiac disease [69], and inflammatory bowel disease [70], all of which are known causes of osteoporosis. High urinary calcium can be idiopathic [71] or due to disorders such as primary hyperparathyroidism [72] and vitamin D toxicity [73]. Interpretation of 24-h urinary calcium requires the use of validated reference ranges. A lower limit of 50–100 mg per 24 h for men and women and an upper limit of 300 mg per 24 h in women and 400 mg per 24 h in men are commonly used. Some laboratories simply report a normal a somewhat arbitrary normal range, such as 100–300 mg per 24 h for men and women [74], although urinary calcium is influenced by variables that include calcium intake, sex, ethnicity, body weight, estrogen status, vitamin D, and parathyroid hormone. A weight-based upper limit of 4 mg per kg per 24 h for men and women has been suggested [75, 76]. A recent study reported reference ranges from pooled data of 3 clinical trials in 959 black and white women on unrestricted diets [74]. The values varied by age and ethnicity, with an overall range of 30–300 mg per 24 h for white women and 10–285 mg per 24 h for black women. It is notable that these data call into question the common use of 50–100 mg per 24 h as the lower limit. The potential for incomplete 24-h urine collections and erroneous measurements [77] has led some clinicians to measure a urine calcium/creatinine ratio in a random urine specimen instead [78]; however, the results of this technique are not interchangeable with a 24-h urine collection and appear to have low sensitivity and specificity for detecting hypercalciuria [79].

## Complete Blood Count

Complete blood count is often recommended based on the potential of detecting anemia due to disorders such as myeloma and

malabsorption of iron with celiac disease or an abnormal white blood cell count with hematological malignancies.

## Laboratory Testing for Specific Disorders

### Hyperthyroidism

Serum thyrotropin (thyroid stimulating hormone) should be considered in patients on thyroid hormone replacement to assure that dosing is correct, and in patients when hyperthyroidism is suspected, since iatrogenic or endogenous excess of thyroid hormone is a risk factor for osteoporosis and fractures [30].

### Hyperparathyroidism

When serum calcium is abnormal or parathyroid disease is suspected, serum PTH should be measured [80, 81]. Primary hyperparathyroidism is diagnosed when PTH is inappropriately high for the level of calcium, which may be high normal, high, or fluctuating between the two. Osteoporosis in a patient with primary hyperparathyroidism is an indication for parathyroid surgery [41]. When serum calcium is normal or low and PTH is high, the patient may have secondary hyperparathyroidism due to causes such as vitamin D deficiency. The cause should be identified and correctly before treatment in initiated. If calcium is normal and secondary hyperparathyroidism has been excluded, the patient may have normocalcemic primary hyperparathyroidism. This has been diagnosed with increasing frequency in recent years as more facilities are routinely measuring PTH in the initial evaluation of patients with osteoporosis [82].

### Celiac Disease

When celiac disease is suspected due to family history, symptoms of malabsorption, or abnormal laboratory findings (e.g., low urinary calcium or iron deficiency anemia that is not otherwise explained), celiac autoantibodies should be measured. Serum tissue transglutaminase and endomysial IgA antibodies have very high sensitivity and specificity for diagnosing celiac disease [83]. A serum IgA level is often measured at the same time, since IgA deficiency may result in falsely low celiac IgA antibody levels. When total IgA is low or undetectable, IgG-based celiac antibodies should be measured.

### Hypogonadism

Declining sex hormone levels are expected in aging men and women. Measurement of a sex hormone level (e.g., serum estradiol in women or serum testosterone in men) is usually not needed in the evaluation of patients with osteoporosis unless it is likely to influence treatment decisions. As examples, when estrogen therapy is being considered for a woman of uncertain menopausal status, hormonal testing might be helpful. For a man under the age of 50 years with osteoporosis, a finding of low testosterone might lead to testosterone replacement therapy, especially in a setting of having both osteoporosis and clinical symptoms of hypogonadism [84].

### Cushing's Syndrome

Screening for subclinical hypercortisolism in patients with osteoporosis may be considered when BMD is unusually low or declines faster than expected, when there is a poor response to therapy, or occurrence of a fragility fracture in a eugonadal man or a premenopausal woman [85]. Assuming exogenous sources of glucocorticoids have been excluded, consider initial screening with one of the following tests: late-night salivary cortisol, 24-h urinary free cortisol, or overnight 1 mg dexamethasone suppression test [86]. An abnormal result should be followed by additional tests.

### Systemic Mastocytosis

Serum tryptase and 24-h urinary N-methylhistamine are often used as screening tests for systemic mastocytosis, with the definitive diagnosis by bone marrow aspiration [87].

### Monoclonal Gammopathy of Uncertain Significance (MGUS) and Myeloma

MGUS and myeloma are associated with adverse skeletal effects [88, 89]. Targeted testing for MGUS and myeloma has been suggested for high-risk groups with osteoporosis and/or fractures. This includes women age < 50 years, men age < 65 years, patients presenting with an "unexpected" new fragility fracture or with fracture history suggesting their risk is higher than that predicted by FRAX or presence of other secondary causes, and women age > 50 years and men age > 65 years with additional "high risk" features such as two or more fragility fractures and fractures under osteoporosis treatment [90]. Screening tests include serum protein electrophoresis, 24-h urinary protein electrophoresis, serum kappa/lambda light chain ratio, complete blood count, and erythrocyte sedimentation rate.

### Inherited Skeletal Diseases

Genetic testing may be helpful for diagnosing or confirming suspected inherited skeletal disorders, such as osteogenesis imperfecta, hypophosphatasia, and X-linked hypophosphatemia [91]. Genetic screening for inherited disorders in patients with idiopathic, severe, or familial osteoporosis appears to be a low yield test [92].

## Other Potentially Helpful Tests

### Bone Turnover Markers

Bone turnover markers (BTMs), such as C-telopeptide (CTX) and procollagen type 1 Intact N-terminal propeptide (P1NP), may identify patients with high or low bone turnover and may influence treatment decisions [93•]. While BTMs cannot be used to determine the cause of osteoporosis, they may be helpful in estimating fracture risk, predicting the rate of bone loss, and assessing the effects of treatment on bone remodeling [94].

### Bone Biopsy

Quantitative histomorphometry with double-tetracycline labeled transiliac bone biopsy is the "gold standard" method for diagnosing osteomalacia and classifying patients with renal osteodystrophy [95, 96•]. With advanced analytical techniques, bone biopsies may also be useful in the assessment of rare bone diseases, such as Paget's disease of bone, osteogenesis imperfecta, fibrous dysplasia, and fibrodysplasia ossificans progressive [97]. However, bone biopsy is rarely used in clinical practice due to its invasive nature, the limited number of individuals performing the procedure and interpreting the specimen, and challenges with cost and insurance coverage.

## Summary

The evaluation of patients with osteoporosis provides an opportunity to recognize other disorders that can mimic osteoporosis and may require treatment that is different than for osteoporosis. It is also an opportunity to better assess fracture risk and to identify conditions needing further evaluation before starting pharmacological therapy to reduce fracture risk. The findings of the osteoporosis evaluation may influence the choice of an initial therapeutic interventions and assessment of the balance of expected benefits and potential risks with different treatment options.

## Declarations

**Conflict of Interest** In the past year, E. Michael Lewiecki has received no direct income from potentially conflicting entities. His employer, New Mexico Clinical Research & Osteoporosis Center, has received research grants from Radius, Amgen, Mereo; income for service on scientific advisory boards or consulting for Amgen, Radius, Alexion, Sandoz, Samsung Bioepis; service on speakers' bureaus for Radius, Alexion; project development for University of New Mexico; and royalties from UpToDate for sections on DXA, fracture risk assessment, and prevention of osteoporosis. He is a board member of the National Osteoporosis Foundation, International Society for Clinical Densitometry, and Osteoporosis Foundation of New Mexico.

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- • Of importance
- •• Of major importance


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