Chapter 3
Diagnosis of Osteoporosis

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Screening for osteoporosis is the initial step in making a diagnosis. Primary care physicians are becoming increasingly attuned to populations at risk for this condition which affects significant numbers of women and older men in the United States and abroad. This chapter will focus on the key components of diagnosis: relevant family and personal history that might contribute to risks for osteoporosis, physical examination findings, imaging, and laboratory studies. All four components are important in the diagnosis and initial care of a patient at risk for osteoporosis as well as a patient in the early phases of established osteoporosis.

Assessment Tools

Medical History and Physical Examination

The National Osteoporosis Foundation (NOF) recommends that all postmenopausal women and men 50 and older should be evaluated for risk of osteoporosis, beginning with a medical history and physical evaluation to determine whether bone mineral density (BMD) testing and/or vertebral imaging are warranted. The history should take into account the following: age, gender, personal history of fractures as an adult and family history of broken bones and osteoporosis, smoking or drinking habits, diet, medications, physical activity, eating disorders, menstrual patterns in women and testosterone levels in men, genetic diseases such as cystic fibrosis and rheumatologic and autoimmune diseases, neurological and musculoskeletal risk factors, and endocrine, gastrointestinal, and hematologic diseases.

The physical examination should include a height and spine check [1]. The results of these screenings are critical in determining whether to move forward with BMD testing.

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Radiographic Studies

Bone Mineral Density (BMD) Testing

As a general guideline, the US Preventive Services Task Force (USPSTF) advises that BMD testing be performed on women age 65 and older and on younger women whose fracture risk is equal to or greater than that of white women, with no additional risk factors [2]. As of 2011, the USPSTF indicates that current evidence is insufficient to weigh the costs/benefits of testing in men [2]. However, the NOF 2014 report advises that men age 50–69 with clinical risk factors for fracture should be tested [1].

Only a bone density test can diagnose osteoporosis before a broken bone actually happens. Measurements of BMD are obtained by dual-energy x-ray absorptiometry (DXA). The DXA machine calculates bone mineral content in grams by summing pixels in a given region viewed by the scanner and dividing that number by the bone area examined in cm^2. A patient's results can be interpreted as a standard deviation from the mean of sex-matched peak bone mass (*T*-score) [3].

The World Health Organization defines osteoporosis as a *T*-score at or below 2.5 standard deviations from the mean BMD of a young normal adult of the same gender under age 30. It is designed for those who have already reached peak bone mass [1]. Another measure known as the *Z*-score employs standard deviations from the mean of age- and sex-matched bone mass. The *Z*-score is often used for patients below age 30 in which peak bone mass has not been achieved, but it is a useful measure for all premenopausal women and men <50 years [4]. A given patient is assigned a *T*- or *Z*-score for a given location (in this case the lumbar spine) based on established norms as illustrated in Fig. 1 [5]. The *T*-score determines whether a patient has normal bone, osteopenia, or osteoporosis as summarized in Table 1 [6].

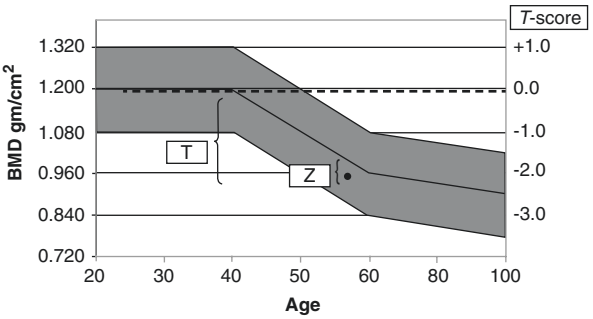

Fig. 1 Normal, osteopenic, and osteoporotic bone by *T* and *Z*-scores (*Source*: National Osteoporosis Foundation [5]. Reproduced with permission)

Table 1 Definitions of normal bone, osteopenia, and osteoporosis by DXA values as established by International Society for Clinical Densitometry (ISCD)

Classification	BMD for young-adult reference population (healthy adult < age 30)	T-score
Normal bone	Within 1 SD of the mean level	−1.0 and above
Osteopenia	Between 1.0 and 2.5 SD below that of the mean level	Between −1.0 and −2.5
Osteoporosis	2.5 SD or more below that of the mean level	At or below −2.5
Severe osteoporosis	2.5 SD or more below that of the mean level	At or below −2.5 with one or more fractures

Source: Mayo Clinic. Tests and Procedures [6]

The *Z*-score is also used to identify high-risk patients, who may not be osteoporotic, but are below expected bone density for their age and should be followed more closely [4]. While there is no specific *T*-score that correlates with fracture threshold, the more negative the *T*-score, the greater the risk [6]. In able-bodied postmenopausal females, several prospective studies indicate that half of patients with incident fractures had baseline BMD assessed by DXA above the diagnostic threshold of osteoporosis [7–9].

Vertebral Imaging

Quite apart from a patient's BMD, the presence of a vertebral fracture is considered by most clinicians to be sufficient for a diagnosis of osteoporosis as well as an important factor in predicting subsequent fractures. Because these fractures tend to be asymptomatic and may be undiagnosed for years, the NOF has established guidelines for the implementation of vertebral imaging tests encompassing women age 65 and older and men age 70 and older if their *T*-score is ≤ -1.5 or below and for women age 70 and men age 80 and older, if their *T*-score at the spine, total hip, and femoral neck is ≤ -1.0 [1].

In patients whose clinical evaluations suggest osteoporosis, radiologists use a lateral thoracic and lumbar spine x-ray or a lateral vertebral fracture assessment; the latter is available on DXA machines and can be performed at the same time as the BMD test [1]. It should be noted, however, that clinicians and radiologists may fail to detect a fracture. Lenchik et al. refer to several studies that demonstrate this failure [10]. For example, a study of 934 hospitalized women aged 60 and over identified moderate to severe vertebral fractures in 14% of the population; only 50% of contemporaneous radiology reports note these fractures [11]. Factors contributing to these failed diagnoses include lack of standardization in the interpretation of radiologic results, inaccurate readings by radiologists, and ambiguous terminology used in the reports [10].

Fracture Risk Assessment Tool (FRAX)

Because osteoporosis may initially present asymptomatically, screenings for osteoporosis in high-risk populations are advisable. While it is optimal that such screening be done as a standard of care, many individuals experience osteoporotic fractures in advance of ever receiving a DXA scan in the community. In fact, initial recognition that individuals are experiencing the effects of osteoporosis often comes when they present in an acute care hospital with a fracture.

To improve screening for fractures, the World Health Organization (WHO) created the Fracture Risk Assessment Tool (FRAX) which calculates the 10-year probability of hip fracture and of a major osteoporotic fracture based on US fracture and mortality rates [10]. The development of FRAX was motivated by the recognition that clinical risk factors are vital in understanding fracture risk. The risk factors used in the FRAX are given in Table 2 [12].

Here, the distinction between diagnosing osteoporosis and assessing fracture risk is important. Whereas FRAX is an assessment tool, BMD measurement remains the most clinically recognized and validated method used to diagnose osteoporosis and predict fractures [13]. However, studies show that 50% of fractures would not be detected if only a BMD measurement were used. The

Table 2 FRAX risk factors

Age
Sex
Weight in kg
Height in cm
Previous fracture: denotes more accurately a previous fracture in adult life occurring spontaneously or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture
Parent with fractured hip: a history of hip fracture in the patient's mother or father
Current smoking
Glucocorticoids: exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than three months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids)
Rheumatoid arthritis: a confirmed diagnosis of rheumatoid arthritis or no such diagnosis
Secondary osteoporosis: a disorder strongly associated with osteoporosis, including type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease
Alcohol: three or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8 to 10 g of alcohol. This is equivalent to a standard glass of beer (285 ml), a single measure of spirits (30 ml), a medium-sized glass of wine (120 ml), or on measure of an aperitif (60 ml)
Bone mineral density (BMD): the manufacturer of DXA scanning equipment used and the actual femoral neck BMD (in g/cm2). Alternatively, the *T*-score based on the NHANES III female reference data can be used

Source: World Health Organization [12]

combination of BMD testing with FRAX provides the most effective means of determining the next steps in managing patients at risk and of providing essential anticipatory guidance [13].

Laboratory Studies

In situations where a patient's *Z*-score (age-matched BMD) is below expected levels, laboratory tests can assist the practitioner in identifying secondary causes of osteoporosis. Suggested studies include complete blood count, serum calcium, vitamin D, thyroid-stimulating hormone (TSH), and liver enzymes. Urine calcium or spot urine calcium/creatinine ratio may detect hypercalciuria, the excessive urinary calcium excretion that is the primary cause of kidney stones [14]. Estrogen plays a central role in osteoblast maturation and production of growth factors to form procollagen as essential building blocks of mature bone [15, 16]. Low estrogen levels are widely known to cause osteoporosis after menopause, but estrogen-deficient states can also be seen in women with premature menopause following total abdominal hysterectomy, with salpingo-oophorectomy (removal of the fallopian tube and ovary) [17, 18] or even among teens and young adults with anorexia nervosa or athletic amenorrhea [19]. In the latter special cases, laboratory investigation should be undertaken even before BMD testing, since early correction of hormonal abnormalities will reduce or even eliminate development of secondary osteoporosis [20, 21]. In men, low testosterone levels can indicate hypogonadism [22].

The best laboratory indicator of vitamin D adequacy is the serum 25-hydroxyvitamin D (D25OH) concentration. There is no consensus on the optimal D25OH concentration for skeletal or extraskeletal health. The Institute of Medicine (IOM) suggests that a level of 20 ng/mL (50 nmol/L) is adequate [23], while Heaney et al. [24] maintain that a minimum level of 32 ng/ml is needed to prevent upregulation of parathyroid hormone and impaired calcium resorption. All patients presenting to an acute hospital with any concern for osteoporotic related disease should at least have a screening involving serum vitamin D 25-OH, serum calcium, and intact parathyroid hormone. These studies are easily obtained in any inpatient facility. Table 3 summarizes initial laboratory workup which should be performed for those with *Z*-scores indicating advanced osteopenia or osteoporosis [14]. These studies will alert clinicians to primary metabolic, endocrine, or renal disorders that predispose patients to osteoporosis.

More advanced laboratory studies are advisable in patients with clinical concern for osteoporosis or in whom screening studies and lab values described above indicate additional workup is needed. If a DXA scan indicates a patient has osteopenia or osteoporosis, the question arises as to whether manifestation of the disease is due to inadequate bone formation, excessive bone loss, or a combination of both. Biochemical bone markers may be used to assess the rate of bone formation and bone resorption. Values for serum N-terminal propeptide (s-CTX) and procollagen type I N-terminal propeptide (P1NP) are not included in the FRAX

Table 3 Initial laboratory workup performed for those with *Z*-scores indicating advanced osteopenia or osteoporosis

Laboratory test	Reason
Complete blood count (CBC)	Marker of general nutrition. Evaluates anemia as source of weakness
Serum total calcium OR	To calculate albumin adjusted calcium. Not universal but may be useful to correct total calcium measurements skewed by abnormal albumin levels
Ionized calcium	More accurate measure of calcium homeostasis
Phosphorus	Detect conditions associated with hypercalcemia, i.e., primary hyperparathyroidism or hypocalcaemia and subsequent secondary hyperparathyroidism causing bone loss
Magnesium	Monitoring needed in relation to calcium and phosphorous
Renal function	To detect renal failure which can affect bone health
Serum creatinine	
Glomerular filtration rate (GFR)	
Liver function tests	Abnormal levels may impair processing of vitamin D
Serum alkaline phosphatase (ALP)	Useful to detect Paget's disease, osteomalacia, fracture healing, metastatic bone disease. May not be sensitive enough to detect changes in bone remodeling in most cases of uncomplicated osteoporosis
25(OH)D	Reflects one measure of overall bone health
Parathyroid hormone (PTH)	To help investigate calcium level abnormality; significantly elevated in setting of severe vitamin D deficiency
Thyroid-stimulating hormone (TSH) +/− free T4	TSH is a direct inhibitor of osteoclasts. Low levels in setting of hyperthyroidism indicate probable bone resorption. Elevated T4 levels are confirmatory for hyperthyroid states which involve increased osteoclastic activity
Blood and erythrocyte sedimentation rate (ESR)	For general health and for inflammatory diseases which often cause bone loss
Consider in selected patients	
Serum protein electrophoresis (SPEP), serum immunofixation, serum-free light chains	To exclude multiple myeloma which causes major bone loss
Total testosterone and gonadotropin in younger men	To exclude multiple myeloma which causes major bone loss
Tissue transglutaminase antibodies (IgA and IgG)	Screening for thyrotoxicosis and hypogonadism
Tryptase	To detect celiac disease
Urinary histamine	To detect celiac disease
Urinary free cortisol level	To detect celiac disease
	To detect Cushing's syndrome
Bone turnover markers	
Serum C-telopeptide (s-CTX) or urine N-telopeptide (u-NTX)	Indicates upregulation of osteoclastic activity which indicates bone resorption
s-P1NP	A measure of osteoblastic activity, representing bone building metabolic activity

Source: Lee and Vasikaran [14]. Adapted with permission.

because the results have been inconsistent due to the use of different markers and different methodologies and leading to calls for greater standardization in these measurements [14].

Bone formation markers include bone-specific alkaline phosphatase (BALP) and P1NP; the latter has the greatest specificity for bone, but all markers have limitations in clinical interpretation [25, 26]. Markers of bone resorption include urine and serum carboxy-terminal cross-linking telopeptide of type I collagen. Both bone formation and resorption markers guide clinicians to types of treatment that are most appropriate for osteoporosis and provide indicators of relative success of pharmacologic interventions, such as bisphosphonate therapy [25, 26]. The above studies may be carried out in either the inpatient or outpatient setting but generally require specialty labs for processing, outside of the immediate clinical setting of the patient. The results are best followed by a practitioner well versed in the literature and intervention strategies since findings may alter treatment choices. Clinicians ordering these tests should become familiar with pretesting requirements since food or medications can interfere with result interpretation.

Early detection is a critical first step in treating osteoporosis. However, further research is needed to provide direct evidence that screening reduces fracture-related morbidity and mortality and to determine the long term outcomes of screened versus non-screened populations. In addition, studies are lacking on the occurrence of fractures in nonwhite and ethnic groups [2].

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