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REVIEW

Osteoporotic Fractures: Diagnosis, Evaluation, and Significance From the International Working Group on DXA Best Practices

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Abstract

Osteoporotic fractures, also known as fragility fractures, are reflective of compromised bone strength and are associated with significant morbidity and mortality. Such fractures may be clinically silent, and others may present clinically with pain and deformity at the time of the injury. Unfortunately, and even at the time of detection, most individuals sustaining fragility fractures are not identified as having underlying metabolic bone disease and are not evaluated or treated to reduce the incidence of future fractures. A multidisciplinary international working group with representation from international societies dedicated to advancing the care of patients with metabolic bone disease has developed best practice recommendations for the diagnosis and evaluation of individuals with fragility fractures. A comprehensive narrative review was conducted to identify key articles on fragility fractures and their impact on the incidence of further fractures, morbidity, and mortality. This document represents consensus among the supporting societies and harmonizes best practice recommendations consistent with advances in research. A fragility fracture in an adult is an important predictor of future fractures and requires further evaluation and treatment of the underlying osteoporosis. It is important to recognize that most fragility fractures occur in patients with bone mineral density T scores higher than −2.5, and these fractures confirm the presence of skeletal fragility even in the presence of a well-maintained bone mineral density. Fragility fractures require further evaluation with exclusion of contributing factors for osteoporosis and assessment of clinical risk factors for fracture followed by appropriate pharmacological intervention designed to reduce the risk of future fracture. Because most low-trauma vertebral fractures do not present with pain, dedicated vertebral imaging and review of past imaging is useful in identifying fractures in patients at high risk for vertebral fractures. Given the importance of fractures in confirming skeletal fragility and predicting future events, it is recommended that an established classification system be used for fracture identification and reporting.

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Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and poor bone quality (eg, architecture, turnover, damage accumulation, and mineralization) leading to reduced bone strength and increased risk of fracture.[1] It constitutes a major public health concern, with 1 in 2 women and 1 in 5 men having a fragility fracture in their remaining lifetime after the age of 50 years.[2] The absolute number and associated illness burden has increased substantially over the past 3 decades such that in 2019 an estimated 178 million new fractures occurred and 455 million people suffered the effects of prior fractures.[3] Today the direct cost of managing fragility fractures worldwide is estimated to be in excess of $100 billion USD ($100,000 million in Europe) with indirect costs close to $200 billion ($200,000 million in Europe).[4-8] As the population ages globally, the personal and economic burden is expected to increase.[4-9]

Despite the widespread availability of reliable instruments for the diagnosis of osteoporosis including fracture risk assessment with or without BMD assessment, as well as the availability of inexpensive, well-tolerated medications proven to reduce fracture risk, most patients who could benefit from treatment do not receive it.[10] This "osteoporosis care gap" reflects the proportion of individuals at high fracture risk, many of whom have already sustained a fragility fracture but have not undergone assessment and treatment for osteoporosis. This care gap is estimated at approximately 70% in Europe[5] and North America and is now recognized as a patient care crisis[11,12] with a global call to action.[13]

Although many factors are responsible for the current care gap, this article will focus on 3 key messages, as follows: (1) fragility fractures in an adult are not "normal" and have significant implications for patient and societal health, (2) dual-energy x-ray absorptiometry (DXA)− vertebral fracture assessment (VFA) and other imaging modalities should be employed to diagnose the presence of fracture and guide treatment to prevent future events,[14] and (3) despite often-reassuring BMD as measured by DXA, fragility fractures confirm impaired bone strength and require evaluation and work-up for osteoporosis. For the purpose of this discussion, a fragility fracture is defined as one that occurs as a result of a force that is less than or equal to that of a fall from standing height (excluding facial, hand, feet, and ankle fractures). Major osteoporotic fracture sites are vertebral, hip, humerus, and forearm fractures.[15] Minor osteoporotic fracture sites are all other locations except face, hands, feet, skull, and ankles.

Various definitions have been proposed for fragility fractures including the European Medicines Agency (EMA) which defines fragility fractures as fractures occurring with low trauma at the hip, spine, pelvis, distal femur, proximal tibia, humerus, forearm, and multiple ribs[16] (Table 1).[15,17-21] This review will focus on strategies for identifying, evaluating, and treating adults with fragility fractures in order to prevent future events. It also provides best practice BMD reporting recommendations for men of all ages as well as premenopausal and postmenopausal women. A subsequent article from the International Working Group on DXA Best Practices (IWG) will address pediatrics and BMD practice.

METHODOLOGY

The multidisciplinary IWG for BMD best practice and reporting recommendations was assembled with representatives from the European Association of Nuclear Medicine (EANM), Canadian Association of Nuclear Medicine (CANM), International Osteoporosis Foundation (IOF), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), International Society for Clinical Densitometry (ISCD), American Society for Bone and Mineral Research (ASBMR), and European Calcified Tissue Society (ECTS). Two of the authors (A.A.K., R.H.A.J.S.) were co-chairs of the IWG. The IWG met virtually every month over the past 2 years and also held an in-person meeting at the ASBMR annual meeting in Vancouver, BC, Canada, in

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October 2023 and addressed all the key clinical questions.

A comprehensive narrative review of the literature was conducted to identify and synthesize key articles on fragility fractures. Multiple search terms for each section were included (including *diagnosis of osteoporosis*, *fracture risk*, *reporting of BMD*, *morbidity and mortality following fracture*). Hand searching of reference lists of relevant articles was also conducted. No limitations were placed on publication date to provide a comprehensive summary of current knowledge. The following sections summarize our findings.

ARTICLE HIGHLIGHTS

- Fragility fractures are indicative of compromised bone strength and unfortunately are not consistently evaluated sufficiently to assess the underlying metabolic bone disease.
- Individuals with fragility fractures can benefit from pharmacological intervention designed to treat the underlying metabolic bone disease.
- Fracture history is critical in the evaluation of fracture risk and in the reporting of bone mineral density studies.
- Most fragility fractures occur in individuals with bone mineral density T scores higher than −2.5 and confirm skeletal fragility. Unfortunately, evaluation and pharmacological intervention is only offered to a small percentage of these individuals.
- Vertebral fracture assessment is valuable in identifying the presence of previously undiagnosed vertebral fractures and assessing the risk of future fractures with minimal radiation exposure, patient inconvenience, and cost. This tool can potentially significantly improve the quality of care provided to patients with osteoporosis.

FRACTURES AND IMPACT ON FUTURE FRACTURE RISK

A fragility fracture is associated with an increased risk of future fractures.[22] There is evidence that both major and minor osteoporotic fractures exhibit relationships with low BMD and increased fracture risk in older adults. Therefore, both should be considered when assessing future fracture risk in older adults[23-29] (Appendix). Patients with multiple prior fractures and low BMD are among those at greatest risk of future fractures.[30,31] In general, the relative risk of fracture following a previous fracture is increased by approximately 2-fold, although the magnitude of risk is affected by several factors. One of these factors is the site of a previous fracture, the strongest effect being seen for hip and vertebral fractures (VFs), with future fracture risk increasing with the number and severity of previous fractures.[22,30-32] A broad range of other fracture sites (particularly the humerus, radius, ankle, and rib) have also been associated with an increased risk of incident fracture.[33,34] Age and sex also influence fracture risk following a fracture; for incident major osteoporotic fracture and in particular hip fracture, the hazard ratio (in comparison to the general population of the same age and sex) decreases progressively with increasing age.[22] The recency of a prior fracture is another important consideration when assessing future fracture risk. The fracture risk is highest in the immediate 1 to 2 years following a major osteoporotic fracture, and this increased fracture risk in the 1- to 2-year period following an index fracture is described as the "imminent fracture risk."[35] The magnitude of this effect has varied according to the cohort studied and the site of prior fracture. For example, after a hip fracture, the hazard ratios for a subsequent hip fracture are notably high based on data from large cohort studies (hazard ratio in women aged 40 years after hip fracture was 46.7 [95% CI, 24.5 to 88.8], and that in men aged 40 years after hip fracture was 92.4 [95% CI, 47.9 to 178.0]).[22] Data from a prospective observational cohort study evaluating 66,874 postmenopausal women found that a prior fracture increased the risk of subsequent fracture, irrespective of whether it was traumatic or nontraumatic. These findings suggest the importance of including both high-trauma and low-trauma fractures in clinical osteoporosis assessments.[24]

CLINICAL RELEVANCE OF VERTEBRAL FRACTURES

Vertebral fractures have consistently been associated with an increase in the imminent fracture risk following fracture.[36,37] They are

TABLE 1. Definitions and Examples of Different Types of Fractures

Fracture type	Description	Examples
Osteoporotic (fragility) fractures	Fractures associated with impaired bone strength	
Major osteoporotic fracture[a]		Clinical, vertebral, hip, humerus, and forearm fractures[15]
Minor osteoporotic fracture		All other fractures except face, hands, skull, feet, ankles
Traumatic fracture	Caused by a significant external impact force or injury	Force greater than a fall from standing height
Pathologic fracture	Occur secondary to altered skeletal physiology and mechanics in the setting of a benign or malignant lesion[17]	Fracture in a bone affected by malignancy or multiple myeloma or other skeletal pathology
Stress fracture	Associated with major recent increase in physical activity or repeated excessive activity with limited rest[18]	Tibia, tarsal navicular, metatarsal stress fracture in runners, fibula, femur, pelvis, and spine[19-21]

[a]The European Medicines Agency (EMA) also designates pelvis, distal femur, proximal tibia, and multiple ribs as major osteoporotic fracture sites.[16]

the most common type of fragility fractures among men and women aged 50 years and older,[38-42] with variable incidence and prevalence among different populations.[3] Vertebral fractures are important because of their potential to cause pain, disability, and increased mortality, as well as increased risk for future VFs within the following year[30] and the risk for non-VFs independent of BMD. Vertebral fractures often do not come to clinical attention and represent a major gap in our ability to identify individuals at high fracture risk.[39-41] The prevalence of VFs increases with age, with approximately 3% in the age group younger than 60 years having a VF identified on imaging to approximately 20% in the age group 70 years or older in women and from approximately 7.5% to 20% in men, respectively.[43]

MORBIDITY AND MORTALITY AFTER A FRACTURE

Fragility fractures are neither normal nor benign events. In many patients, fractures require surgical intervention and associated adverse effects include anesthetic complications, postoperative pain, bleeding, infection, and thromboembolic complications. Successful surgical outcomes depend on the capacity of the bone to remodel and heal microdamage and macrodamage via callus formation and sustain new loads placed at the site of bone-implant interfaces and the ability of the patient to rehabilitate and regain mobility and strength.[44] Among the more common fractures requiring surgical intervention, those involving the hip can be most challenging in patients with preexisting osteoporosis. In prospective trials, of patients who have healing complications or implant failure following an intertrochanteric hip repair, 76% had moderate or severe osteoporosis.[45] Pain, surgery, immobility, and consequent deconditioning often result in the need for prolonged rehabilitation. Regardless of prefracture functional status, up to 50% of patients will not return to prior mobility 1 year following hip fracture.[46] Approximately 20% to 65% of patients living independently prior to hip fracture will require assistance in completing prefracture activities of daily living.[47,48] A multidisciplinary approach to postfracture care has been found to reduce length of hospital stay and mortality. Fracture liaison services as well as orthogeriatric co-management are of value in reducing morbidity and mortality, particularly in older individuals with hip fracture.[49-52]

Postfracture mortality is highest in the first year following the fracture, particularly following clinical VFs or hip fractures.[5,53-59] Other hip fracture observational studies have reported mortality rates in the first year being almost twice that seen at 2 years after hip fracture in clinical trials, reflecting

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the impact of age, frailty,[60] and multiple comorbidities.[55-57,61,62] Nonhip fractures are also associated with higher rates of mortality both short- and long-term in comparison to the general population.[41,63-66] In the 5 to 10 years following fracture, the mortality rate compared to the general population remains 2 to 3 times higher, particularly in the event of another fracture.[67]

TREATMENT EFFECTS ON FRACTURE

Bisphosphonates, compared with a placebo, have been found to reduce hip fracture risk over 36 to 48 months (risk ratio [RR], 0.64; 95% CI, 0.50 to 0.82), and denosumab over 36 months also reduced hip fracture risk (RR, 0.61; 95% CI, 0.37 to 0.98).[68] A recent network meta-analysis evaluating 73 osteoporosis trials reported a protective effect of bisphosphonates, denosumab, parathyroid hormone receptor agonists, and romosozumab for hip fractures compared with placebo but not selective estrogen receptor modulators.[69] In females with a high risk of fracture due to age and fracture history, the sequential use of romosozumab followed by alendronate was more effective than alendronate alone in reducing hip fracture risk for 24 months (RR, 0.62; 95% CI, 0.42 to 0.91).

Treatment with bisphosphonates for 12 to 36 months and denosumab for 36 months markedly reduced the risk of clinical VFs by 54% to 68% compared with placebo. Teriparatide exhibited a 76% risk reduction at 17 months, and romosozumab had an 82% reduction in the risk of clinical VFs at 12 months.[68]

ECONOMIC COSTS

The economic costs associated with fracture care are greatest in the year following a fracture. The total economic cost is estimated to be between one-fourth and one-half trillion US dollars today, similar or greater than costs associated with cancer or cardiovascular disease.[4-8] In particular, hip fractures and VFs are associated with the highest health care cost burden.[5] A recent European report on 29 countries with a population similar to the United States and Canada suggests that more than 4 million fractures occur annually (nearly 10 per minute) in this region, with a direct cost of almost €57 billion per year.[5] These numbers are projected to grow substantially as the population ages and will be a much greater burden in Asia in coming decades, where 50% of the world's hip fractures are expected to occur by 2050. In Europe and North America, data show that the burden and cost of fractures is similar to cardiovascular disease and greater than many cancers, although osteoporosis receives considerably less attention.[70-72]

BMD BEST PRACTICES IN ADULTS WITH FRACTURE

The original World Health Organization definition of osteoporosis is based on the BMD T score at the femoral neck, total hip, or lumbar spine, with the femoral neck being the reference site recommended by the World Health Organization and international societies dedicated to advancing skeletal health.[73] Thus, a T score of −2.5 or lower at the lumbar spine, femoral neck, total hip, or 1/3 radial site in postmenopausal women or men aged 50 years or older has become the diagnostic criterion for osteoporosis.[25,74] Further detail regarding the rationale for the use of manufacturers' specific databases for calculating the lumbar spine T scores in both men aged 50 years or older and postmenopausal women has been published.[29]

More recently, inclusion of fracture occurrence in the definition of osteoporosis has been recommended given that 60% of osteoporotic fractures occur in patients with a T score higher than −2.5.[75,76]

Therefore, the diagnosis of osteoporosis can be made by (1) BMD assessment by DXA, (2) the presence of a fragility fracture, or (3) fracture risk assessment tools beyond DXA (eg, VFA) (Table 2).[25-28,74,77-79]

BEYOND BMD: UTILIZATION OF IMAGING MODALITIES TO DIAGNOSE FRACTURES

Currently, VF reporting is often suboptimal, sometimes noting that vertebral body heights are moderately or mildly decreased,

TABLE 2. Fracture Risk Categories as Defined by Different Organizations

Risk category	Very high fracture risk	High fracture risk	Intermediate fracture risk	Imminent fracture risk
AACE[25]	• Recent fracture (eg, within the past 12 months) • Fractures while undergoing approved osteoporosis therapy • Multiple fractures • Fractures while taking drugs causing skeletal harm (eg, long-term glucocorticoids) • Very low T score (less than −3.0) • High risk for falls or history of injurious falls • Very high fracture probability by FRAX (MOF >30%, hip fracture >4.5%)	• Patients with osteoporosis with no prior osteoporotic fracture and those who are not at a very high fracture risk are considered to be at a high risk for fracture	• Not categorized by AACE	• Not categorized by AACE
Endocrine Society[74]	• Severe osteoporosis (ie, T score at the hip or spine of −2.5 or lower and fractures) • Multiple vertebral fractures	• Prior spine or hip fracture • BMD T score at the hip or spine of −2.5 or lower • 10-Year hip fracture risk ≥3% or risk of MOF ≥20% measured by country-specific guidelines	• No prior hip or spine fractures • BMD T score at the hip and spine both above −2.5 • 10-year hip fracture risk <3% or risk of MOF <20%, measured by country-specific guidelines	• Not defined
IOF/ESCEO[26,77-79]	• Age-dependent FRAX probability threshold	• Age-dependent FRAX probability threshold	• Age-dependent FRAX probability threshold	• The risk of subsequent fracture is highest in the first 2 years after an initial fracture
SOGC[27]	• Recent fracture within the past 12 months • Multiple fragility fractures • MOF risk >30% or hip fracture risk >4.5% as measured by FRAX or CAROC	• ≥20% risk of MOF over the next 10 years or ≥3% risk of hip fracture as measured by FRAX or CAROC	• 10%-20% Risk of MOF over the next 10 years as measured by FRAX or CAROC	• The risk of subsequent fracture, after an osteoporotic fracture, is highest in the next 12-24 months
NAMS[28]	• Prior and especially recent fractures • Very low BMD (T score below −3.0) • Sustained fractures or BMD declines while taking anti-remodeling therapy	• BMD T score of −2.5 or lower in the LS or TH or FN • History of vertebral (spine) or hip fracture, irrespective of BMD or other risk factors • Low BMD (T score between −1.0 and −2.5) and any of the following:	• BMD T score of −2.5 or lower in the LS or TH or FN with no other risk factors	• Similar to very high fracture risk

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TABLE 2. Continued

Risk category	Very high fracture risk	High fracture risk	Intermediate fracture risk	Imminent fracture risk
		(1) History of fracture of proximal humerus, pelvis, or distal forearm (2) History of multiple fractures at other sites (excluding face, feet, and hands) (3) Increased fracture risk using FRAX country-specific thresholds		

AACE, American Association of Clinical Endocrinology; BMD, body mass index; CAROC, Canadian Association of Radiologists and Osteoporosis Canada; FN, femoral neck; FRAX, fracture risk assessment tool; IOF, international osteoporosis foundation; LS, lumbar spine; MOF, major osteoporotic fracture; NAMS, North American Menopause Society; SOGC, Society of Obstetricians and Gynaecologists of Canada; TH, total hip.

without mentioning the word *fracture*. Patient care could be significantly enhanced by using established classification systems, such as that of Genant, McCloskey, or a modified algorithm-based qualitative method (grade 1, 2, or 3).[80-82]

If the vertebral body appearance is consistent with a fragility fracture, it should be clearly described as a fracture on the report and nonspecific terms such as a *deformity* or *wedging* should not be used. Utilization of either morphology or morphometry is of value in identifying VFs, enabling clinicians to appropriately evaluate fracture risk and initiate drug therapy.

Improvements in image resolution with DXA technology now enable DXA to be used for VFA.[83,84] Vertebral fracture assessment enables a rapid assessment of the lateral spine and can be performed at the same visit as the BMD study by DXA. Vertebral fracture assessment is a reliable technique of value in detecting VFs, particularly moderate and severe fractures.[85] Moreover, VFA is relatively inexpensive, with low radiation exposure compared with standard radiography.

Indications for VFA vary across guidelines but include patients at high risk for fractures based on a very low T score, back pain,[86] height decreased by 4 cm or more over the lifetime or 2 cm under medical observation,[87] glucocorticoid use,[88] and/or advanced age.[89]

Vertebral fracture assessment may also be considered in those with long-standing poorly controlled diabetes (type 1 and type 2) because of the increased risk of fractures secondary to impaired bone quality.[90-92] As discovery of a previously undetected VF may influence fracture risk, more widespread use of this approach is warranted and would be helpful for clinicians. The quality of VFA reporting can be enhanced by ensuring that operators and reporting physicians receive standardized training because the assessment is subjective.[84] If VFA is not available, then spinal radiography can be completed as appropriate to identify VFs when indicated.

If a VF is identified by imaging, further evaluation is required in order to exclude additional skeletal pathology and date the fracture.[93,94] Reviewing previous imaging is imperative. Magnetic resonance imaging with short inversion time inversion recovery (STIR) sequence is able to differentiate between osteoporotic and pathologic fractures, establish recency of fracture, and also better define the anatomy of the fracture than standard radiography.[94,95] Bone scanning is also of value in determining the acuity of fractures.[96] Computed tomography (CT) can identify acute fractures based on morphologic features.[97] Identification of VFs depends on the skill of the interpreter.[98]

TABLE 3. Important Factors Contributing to Bone Loss

Diseases/conditions
• Hypogonadism (primary and secondary)
• Primary hyperparathyroidism
• Thyrotoxicosis
• Hypercortisolism
• Growth hormone deficiency
• Diabetes (type 1 and type 2)
• Cystic fibrosis
• Chronic obstructive pulmonary disease
• Neuromuscular disorders
• Osteomalacia
• Anorexia nervosa
• Myeloproliferative disorders
• Malignancy
• Inflammatory rheumatic diseases (rheumatoid arthritis, systemic lupus erythrematosis, ankylosing spondylitis)
• Osteogenesis imperfecta
• Hypophosphatemia
• Hypophosphatasia
• Renal disease
• Idiopathic hypercalciuria
• Thalassemia major
• Mastocytosis
• HIV infection
Malabsorptive states
• Celiac disease
• Hepatic disorders (eg, primary biliary cirrhosis)
• Inflammatory bowel disease
• Postgastrectomy and bariatric surgery
Medications
• Glucocorticoids
• Thyroxine (excessive)
• Anticonvulsants (eg, phenytoin, phenobarbital)
• Heparin (long-term)
• Lithium
• Cytotoxic chemotherapy
• Gonadotropin-releasing hormone agonists
• Depo medroxyprogesterone acetate
• Proton pump inhibitors
• Protease inhibitors
• Thiazolidinediones
• Sodium-glucose cotransporter 2 inhibitors
• Aromatase inhibitors
• Androgen deprivation therapy
• Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
• Calcineurin inhibitors
• Antiretroviral therapy
Miscellaneous
• Alcohol
• Smoking
• Pretransplant and posttransplant status

Requesting a review of previous studies, including spine radiographs, CT scans, or previous magnetic resonance images, can be helpful in determining the acuity of the VF and for excluding additional pathology. This is of value in establishing an appropriate diagnosis and developing a plan of management. Care can be significantly enhanced through identification of missed fractures and diseases resulting in VFs.

BONE QUALITY ASSESSMENT

Bone quality, distinct from bone quantity, reflects the intrinsic biomechanical characteristics that contribute to bone strength in addition to bone quantity. These characteristics are not considered in the quantification of bone mass through DXA. Quantitative

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CT and high-resolution peripheral quantitative CT are the 2 most used CT techniques for bone quality evaluation.[99] Trabecular bone score, a DXA-based software applied to lumbar spine images, is another tool for assessing bone quality. It is also necessary to consider biochemical and clinical factors that impact bone quality and include the presence of diabetes mellitus,[100,101] primary hyperparathyroidism,[102-104] hypercortisolism,[105] and renal osteodystrophy, which are associated with impaired bone quality.

EVALUATION AND WORK-UP OF PATIENTS WITH FRACTURE

Following a fragility fracture, it is essential to evaluate further and exclude contributing factors for osteoporosis or the presence of other metabolic bone diseases (Table 3) and initiate appropriate treatment. A contributing factor for osteoporosis may be identified in 32% to 85% of previously undiagnosed women.[106,107] The laboratory investigations completed to exclude an underlying cause for the osteoporosis are listed in Table 4.

Falls are also associated with an increased risk of fracture and their presence should be determined and further evaluated.[108-110] Similarly, osteosarcopenia is associated with an increased relative risk of fracture and requires further evaluation.[111,112]

There are some populations for whom special attention is required to determine the etiology and guide management. A fragility fracture in a premenopausal woman or younger man indicates impaired bone strength and requires further evaluation. The majority of such fractures are due to an underlying disease.[113-115] In many countries, such evaluation is appropriately undertaken in primary care; however, referral to a specialized center may also be appropriate in more complex cases[25] (Table 5).

In women, the 2 key factors that determine the achievement and maintenance of bone strength are gonadal status and body weight.[113] Clinical estrogen deficiency (eg, central hypogonadism "low leutinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol" or primary ovarian failure "high LH, FSH, low estradiol" in the presence of oligomenorrhea or amenorrhea in women) or subclinical estrogen deficiency (high LH and FSH, normal estradiol in the presence of regular monthly periods) can contribute to achieving a lower peak bone mass or to the development of bone loss in premenopausal years.[113] Other important factors that can result in the development of osteoporosis include diseases associated with impaired bone formation or excessive bone loss or mineralization abnormalities as well as drugs that can increase the risk of osteoporosis and fragility facture.

The clinical evaluation of fragility fractures or low BMD in a premenopausal

TABLE 4. Work-up for Low Bone Mineral Density

Laboratory investigations
• Serum calcium (corrected for albumin)
• Complete blood cell count
• Erythrocyte sedimentation rate
• Phosphate
• Magnesium
• Liver function tests (alkaline phosphatase)
• Thyrotropin
• Estradiol, follicle-stimulating hormone, prolactin (in premenopausal women)
• Total and free testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin (men)
• 25-hydroxyvitamin D
• Parathyroid hormone
24-Hour urine collection for
• Calcium
• Creatinine
• Free cortisol
Additional investigations as applicable
• Antigliadin antibodies
• Anti-endomysial antibodies
• Bone markers P1NP and CTX
• 1-mg Dexamethasone suppression test

TABLE 5. Suggested Criteria for Referral to an Osteoporosis Specialist From the AACE Guidelines[25]

Criteria	Recommendation
Patients with normal BMD who experience fragility fractures Patients with recurrent fractures or continued bone loss while receiving therapy without obvious treatable causes of bone loss Patients with unexpectedly low BMD or with unusual features of osteoporosis such as young age, unexplained artifacts on bone density tests, and unexplained laboratory studies, including high or low ALP levels and/or low phosphorus Patients with a diagnosis of osteoporosis in the presence of a metabolic bone disease or a disease that may affect bone health (eg, hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin) Patients with a condition that complicates management (eg, decreased kidney function, hyperparathyroidism, or malabsorption)	Referral to a clinical endocrinologist or other osteoporosis specialist should be considered
Patients who experience fragility fractures	Referral to an osteoporosis specialist or a fracture liaison team, if available, should be considered

ALP, alkaline phosphatase; BMD, bone mineral density.

woman requires a careful review of gonadal status as well as exclusion of diseases or drugs that can affect bone health. Body weight, both current and past, requires careful assessment—a history of anorexia nervosa may have impaired the achievement of genetically determined peak bone mass or contributed to bone loss in the young adult years. Bone mineral density evaluation is only advised in premenopausal women sustaining a fragility fracture or receiving drug therapy associated with an increased risk of fracture or those affected by diseases associated with impaired bone strength.[27]

Bone density in young women follows a gaussian distribution, with 17% of young women having a T score lower than −1.0.[116] In premenopausal women, low BMD may reflect normal variation in BMD or achievement of a lower than optimal peak bone mass owing to genetic and environmental factors, including calcium intake, lack of exercise, smoking, or excessive alcohol intake.[115,117,118]

The relationship between BMD and fracture risk in young eugonadal individuals is not well defined due to insufficient prospective data. The approach to osteoporosis diagnosis thus varies across different guidelines. Low BMD should be investigated as it may be due to medical conditions associated with bone loss that require diagnosis and intervention.

For premenopausal women and men younger than 50 years, the ISCD recommends evaluating the age- and race-matched Z scores. A Z score of −2.0 or lower is considered low and further evaluation is required to exclude a cause for the low BMD. It is reported as being "below the expected range for age."[119] The IOF defines osteoporosis in young adults as a T score lower than −2.5 at the lumbar spine or hip in association with a chronic disease known to have adverse effects of bone metabolism.[120]

Young men achieve a higher peak bone mass than young women by approximately 20% and have a higher cross-sectional area at both central and peripheral skeletal sites in comparison to young women by approximately 30%.[121] Because men achieve a higher peak bone mass than women, they have bigger and stronger bones throughout life. Also, the rate of bone loss is lower in men than in women[115,122] and men therefore experience fewer fractures than women.[123]

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Bone mineral density measured by DXA can result in overestimation of BMD in individuals who are taller than the average adult and underestimate BMD in petite individuals. This size artifact should be considered when evaluating BMD in those at extremes of height.[124] In addition, caution is required when interpreting BMD changes in the presence of significant weight gain or weight loss.[125] Fracture risk is not quantified with the fracture risk assessment tool in those younger than 40 years; however, the presence of a VF or a hip fracture or multiple fragility fractures denotes a high fracture risk regardless of age.

CONCLUSION

Currently, most individuals experiencing a fragility fracture do not receive appropriate assessment and treatment to reduce the risk of a further fracture. This care gap is partly due to inadequate identification of individuals at high fracture risk and underreporting of fractures, resulting in significant excess morbidity and mortality. Vertebral fracture assessment is of value in identifying the presence of VF and assessing risk of future fracture. Individuals who have sustained a fracture require further clinical evaluation for an underlying cause and to exclude the possibility of a pathologic fracture due to malignancy or infection or other disease state. The presence of a contributing factor for the underlying osteoporosis or an underlying metabolic bone disease requires evaluation and treatment. Bone mineral density reporting requires careful review of the fracture history and incorporation of this data in the fracture risk assessment.

POTENTIAL COMPETING INTERESTS

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMD,** bone mineral density; **CT,** computed tomography; **DXA,** dual-energy x-ray absorptiometry; **FSH,** follicle-stimulating hormone; **IWG,** International Working Group on DXA Best Practices; **LH,** luteinizing hormone; **RR,** risk ratio; **VF,** vertebral fracture; **VFA,** vertebral fracture assessment

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