Chapter 12--OSTEOPOROSIS: CLINICAL EVALUATION

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ABSTRACT

The identification of a patient at high risk of fracture should be followed by evaluation for factors contributing to low bone mass, skeletal fragility, falls, and fractures. Components of the evaluation include a bone density test, osteoporosis-directed medical history and physical exam, laboratory studies, and possibly skeletal imaging. A bone density test with dual energy X-ray absorptiometry (DXA) helps with diagnostic classification, assessment of fracture risk, and provides a baseline for monitoring the skeletal effects of treatment. FRAX is a fracture risk algorithm that included input of femoral neck bone mineral density measured by DXA. The DXA T-score and FRAX estimation of fracture risk are used with clinical practice guidelines to determine whether treatment is indicated. The medical history may reveal underlying causes of osteoporosis (e.g., nutritional deficiencies, gastric surgery, medications with adverse skeletal effects) and important risk factors for fracture (e.g., past history of fracture, family history of osteoporosis, or recent falls). Physical exam may show skeletal deformities due to unrecognized fractures (e.g., loss of height, kyphosis, or diminished rib-pelvis space), identify possible secondary causes of skeletal fragility (e.g., blue sclera with osteogenesis imperfecta, urticarial pigmentosa with systemic mastocytosis, or bone tenderness with osteomalacia), and help to recognize patients with poor balance and frailty that might lead to falls. Laboratory studies may show potentially reversible abnormalities (e.g., vitamin D deficiency, hypocalcemia, or impaired kidney function) that must be assessed and corrected, if possible, before starting pharmacological therapy. Disorders other than osteoporosis, requiring other types of treatment, may be found; for example, low serum alkaline phosphatase suggests hypophosphatasia, M-component may be due to multiple myeloma, or hypocalciuria due to celiac disease. There are important safety considerations that can be derived from a pre-treatment assessment, as well. A patient with a blood clotting disorder should not be treated with raloxifene, a history of esophageal stricture is a contraindication for oral bisphosphonates, and previous skeletal radiation therapy precludes treatment with teriparatide. Skeletal imaging may be helpful when a fracture, malignancy, or Paget's disease of bone is suspected. Bone biopsy is rarely preformed in clinical practice, but may be helpful in some situations, such as when it is necessary to determine the underlying bone disease in a patient with stage 5 chronic kidney disease.

INTRODUCTION

Osteoporosis is a common disease characterized by low bone strength that results in an increased risk of fracture (1). Fractures are associated with serious clinical consequences, including long-term disability, increased risk of death, and high healthcare costs. Early identification and intervention with patients at high risk for fracture is needed to reduce the burden of osteoporotic fractures (2). The management of a patient with a confirmed diagnosis of osteoporosis or low bone mass (osteopenia) includes assessment of fracture risk, evaluation for secondary causes of skeletal fragility, making decisions on initiation of treatment, and identification of all relevant clinical factors that may influence

patient management. This is a review of the key components in the care of patients with osteoporosis prior to treatment.

DIAGNOSIS OF OSTEOPOROSIS

The World Health Organization (WHO) diagnostic classification (Table 1) (3) is made by bone mineral density (BMD) testing with dual-energy X-ray absorptiometry (DXA) using the T-score, calculated by subtracting the mean BMD (in g/cm^2) of a young-adult reference population from the patient's BMD and dividing by the standard deviation (SD) of the young-adult reference population. The International Society for Clinical Densitometry (ISCD) recommends that BMD be measured at the lumbar spine (L1L4), total hip, and femoral neck, with the 33% radius (1/3 radius) being measured when the lumbar spine and/or hip cannot be measured (e.g., obese patient who exceeds weight limit of table) or is invalid (e.g., patient with lumbar laminectomy) (4). Osteoporosis cannot be diagnosed by BMD measurement at skeletal sites other than lumbar spine, total hip, femoral neck, and 33% radius or with technologies other than DXA. The quality of DXA instrument maintenance, acquisition, analysis, interpretation, and reporting is important in obtaining valid results that can be used for making appropriate clinical decisions (4,5). In a patient with a fragility fracture, a clinical diagnosis of osteoporosis may be considered independently of BMD results, assuming that other causes of skeletal fragility (e.g., osteomalacia) are not responsible for the fracture. Establishing a diagnosis of osteoporosis is clinically useful because it facilitates communication among healthcare providers and patients concerning a disease with potentially serious consequences; in some countries, such as the United States (US), a diagnosis is necessary in order to select a numerical code for submission of insurance claims for reimbursement for medical services. The US National Bone Health Alliance (6) has recommended that osteoporosis be diagnosed in postmenopausal women and men over the age of 50 years in any of the following circumstances: T-score ≤ −2.5 at the lumbar spine or hip; low-trauma hip fracture; osteopenia by BMD with a low-trauma vertebral, proximal humerus, pelvis, or, in some cases, distal forearm fracture; and when FRAX shows high fracture risk (10-year probability of major osteoporotic fracture ≥ 20% or 10-year probability of hip fracture ≥ 3%).

Table 1. World Health Organization criteria for classification of patients with bone mineral density measured by dual-energy X-ray absorptiometry (3)**.**

Classification	T-score
Normal	-1.0 or greater
Low bone mass (osteopenia)	Between 1-.0 and .2.5
Osteoporosis	-2.5 and below
Severe osteoporosis	-2.5 and below + fragility fracture

The National Osteoporosis Foundation (NOF) indications for BMD testing in the US (7), which are similar to the ISCD Official Positions (4), are listed in Table 2. BMD testing should be done only when it is likely to have an influence on patient management decisions. Other organizations and other countries with different economic resources and health care priorities have used a variety of methodologies to develop alternative recommendations (8-10).

Table 2. National Osteoporosis Foundation recommends that bone mineral density testing be performed at DXA facilities using accepted quality assurance procedures for the following individuals (7).

- All women age 65 and older and men age 70 and older,
- Postmenopausal women and men above age 50-69, based on risk factor profile
- Postmenopausal women and men over age 50 who have had an adult age fracture, to diagnose and determine the degree of osteoporosis

FRACTURE RISK ASSESSMENT

There is a robust correlation between BMD and fracture risk, with approximately a 2-fold increase in fracture risk for every 1 SD decrease in BMD (11). However, many or most patients with a hip fracture have a T-score better than -2.5 (12); although fracture risk is higher in patients with very low BMD, there are numerically many more patients with a T-score better than -2.5 than with a T-score of -2.5 or worse, therefore numerically more fractures in those with higher T-scores. The presence of clinical risk factors (CRFs) that are independent of BMD, particularly age and prior fracture, can help identify patients at high risk for fracture by providing information on fracture risk that is complementary to BMD. The NOF has provided an extensive list of CRFs (Table 3) for osteoporosis and fractures. Since most fractures occur as a result of a fall, it is helpful to recognize risk factors for falling (Table 4) so that appropriate interventions can be made, when possible, to reduce the chances of falling.

Table 3. Conditions, diseases and medications that cause or contribute to osteoporosis and fractures (7)**.**

Lifestyle factors
Low calcium intake
Vitamin D insufficiency
Excess vitamin A
High caffeine intake
High salt intake
Aluminum (in antacids)
Alcohol (3 or more drinks/d)
Inadequate physical activity
Immobilization
Smoking (active or passive)
Falling
Thinness

Genetic factors
Cystic fibrosis
Homocystinuria
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Hypophosphatasia
Parental history of hip fracture
Gaucher's disease
Idiopathic hypercalciuria
Porphyria
Glycogen storage diseases
Marfan syndrome
Riley-Day syndrome
Hemochromatosis
Menkes steely hair syndrome
Hypogonadal states
Androgen insensitivity
Hyperprolactinemia
Turner's & Klinefelter's syndromes
Anorexia nervosa and bulimia

Panhypopituitarism
Athletic amenorrhea
Premature ovarian failure

Endocrine disorders
Adrenal insufficiency
Diabetes mellitus
Thyrotoxicosis
Cushing's syndrome
Hyperparathyroidism

Gastrointestinal disorders
Celiac disease
Inflammatory bowel disease
Primary biliary cirrhosis
Gastric bypass
Malabsorption
GI surgery
Pancreatic disease

Hematologic disorders
Hemophilia
Multiple myeloma
Systemic mastocytosis
Leukemia and lymphomas
Sickle cell disease
Thalassemia

Rheumatic and autoimmune diseases
Ankylosing spondylitis
Lupus
Rheumatoid arthritis

Miscellaneous conditions and diseases
Alcoholism
Emphysema
Muscular dystrophy
Amyloidosis
End stage renal disease
Parenteral nutrition
Chronic metabolic acidosis
Epilepsy
Post-transplant bone disease
Congestive heart failure
Idiopathic scoliosis
Prior fracture as an adult
Depression
Multiple sclerosis
Sarcoidosis

Medications
Anticoagulants (heparin)
Cancer chemotherapeutic drugs
Gonadotropin releasing hormone agonists
Anticonvulsants

Cyclosporine A and tacrolimus
Lithium
Aromatase inhibitors
Depo-medroxyprogesterone
Barbiturates
Glucocorticoids (≥ 5 mg/d of prednisone or equivalent for ≥ 3 mo)

VERTEBRAL FRACTURE ASSESSMENT (VFA)

VFA is a method for imaging the thoracic and lumbar spine by DXA for the purpose of detecting vertebral fracture deformities. Identification of a previously unrecognized vertebral fracture may alter diagnostic classification, change estimation of fracture risk, and influence treatment decisions (13). VFA compares favorably with standard radiographs of the spine, with good correlation for detecting moderate (grade 2) and severe (grade 3) vertebral fractures, a smaller dose of ionizing irradiation, greater patient convenience (i.e., it may be done at the same visit and with the same instrument as BMD testing by DXA), and lower cost. In a study of women age 65 and older, using the Genant semi-quantitative (SC) method of classifying vertebral deformities (14), the sensitivity of VFA for diagnosing moderate and severe vertebral fractures was 87-93%, with a specificity of 93-95% (15). Indications for vertebral imaging are listed in Table 4. Optimal use of DXA and VFA requires training and adherence to well established quality standards (4).

Table 4. International Society for Clinical Densitometry (ISCD) indications for lateral spine imaging by standard radiography or vertebral fracture assessment (VFA). The ISCD Official Positions (4) state that vertebral imaging is indicated when the T-score is < -1.0 and one or more of the following is present:

- Woman age ≥ 70 years or man age ≥ 80 years
- Historical height loss > 4 cm (1.5 inches)
- Self-reported but undocumented prior vertebral fracture
- Glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months

Table 5. Risk factors for falls adapted from guidelines of the National Osteoporosis Foundation (7). The presence of any of these risk factors should trigger consideration of further evaluation and treatment to reduce the risk of falls and fall-related injuries.

Environmental risk factors
Lack of assistive devices in bathrooms
Loose throw rugs
Low level lighting
Obstacles in the walking path
Slippery outdoor conditions
Medical risk factors
Age
Anxiety and agitation
Arrhythmias
Dehydration
Depression
Female gender
Impaired transfer and mobility
Malnutrition

Medications causing over-sedation (narcotic analgesics, anticonvulsants, psychotropics)
Orthostatic hypotension
Poor vision and use of bifocals
Previous fall
Reduced problem solving or mental acuity and diminished cognitive skills
Urgent urinary incontinence
Vitamin D insufficiency [serum 25-hydroxyvitamin D (25(OH)D) < 30 ng/ml (75nmol/L)]

Neurological and musculoskeletal risk factors

Kyphosis
Poor balance
Reduced proprioception
Weak muscles

Other risk factors

Fear of falling

QUALITY OF DXA AND VFA

DXA and VFA should be performed by well-trained and experienced staff operating an instrument that has been maintained and calibrated according to the manufacturer's standards. Precision assessment and LSC calculation by each DXA technologist are required in order to make quantitative comparisons of serial BMD measurements. The use of the correct scan mode and proper patient positioning is important for accurate BMD measurements and essential for serial comparisons of BMD. VFA should be done by a technologist properly trained in acquisition techniques and interpreted by a clinician familiar with methods of diagnosing vertebral fractures using this technology. Bone densitometry facilities should be supervised by a clinician who knows current methods for BMD measurement and fully understands the standards for quality control, interpretation, and reporting of the findings. Poor quality studies may result in inappropriate clinical decisions, generate unnecessary healthcare expenses, and be harmful to patients (5).

TECHNOLOGIES FOR ASSESSMENT OF SKELETAL HEALTH

DXA. Devices that measure or estimate BMD differ according to their clinical utility, cost, portability, and use of ionizing radiation (Table 6. DXA is the "gold standard" method for measuring bone density in clinical practice (16). There is a strong correlation between mechanical strength and BMD measured by DXA biomechanical studies (17). In observational studies of untreated patients, there is a robust relationship between fracture risk and BMD measured by DXA (11). The WHO diagnostic classification of osteoporosis is based primarily on reference data obtained by DXA (3), and femoral neck BMD provides input into the FRAX algorithm . Most randomized clinical trials showing reduction in fracture risk with pharmacological therapy have selected study according to BMD measured by DXA (18). There is a relationship between fracture risk reduction with drug therapy and increases in BMD measured by DXA (19). Accuracy and precision of DXA are excellent (20). Radiation exposure with DXA is very low (21). BMD of the 33% (one-third) radius, measured either by a dedicated pDXA device or a central DXA instrument with appropriate software, may be used for diagnostic classification with the WHO criteria and to assess fracture risk, but is generally not clinically useful in monitoring the effects of treatment (21). DXA measures bone mineral content (BMC in grams [g]) and bone area (cm^2), then calculates areal BMD in g/cm^2 and derives parameters, such as the T-score and Z-score. DXA is used for diagnostic classification, assessment of fracture risk, and for monitoring changes in BMD over time.

Table 6. Devices for measuring or estimating bone mineral density (BMD). Clinical applications of different technologies are listed with approximate comparison of associated radiation exposure and cost, with 0 = none, + = low, ++ moderate, +++ = highest.

DXA	pDXA	QUS	QCT	pQCT

Yes	**Diagnostic classification***	Limited**	No	No	No
Areal BMD	**Measurement**	Areal BMD	SOS, BUA	Volumetric BMD	Volumetric BMD
Yes	**Prediction of fracture risk**	Yes	Yes	Yes	Yes
Yes	**Monitoring changes over time**	No	No	Yes	No
++	**Ionizing radiation**	+	0	+++	++
++	**Cost**	+	+	+++	++

DXA = dual-energy X-ray absorptiometry; pDXA = peripheral DXA; QUS = quantitative ultrasound; QCT = quantitative computed ultrasound; pQCT = peripheral QCT; SOS = speed of sound; BUA = broadband ultrasound attenuation
* World Health Organization classification
**pDXA of the distal one-third radius (33% radius) may be used with the WHO classification

Quantitative ultrasound (QUS). QUS devices emit inaudible high frequency sound waves in the ultrasonic range, typically between 0.1 and 1.0 megahertz (MHz). The sound waves are produced and detected by means of high-efficiency piezoelectric transducers, which must have good acoustical contact with the skin over the bone being tested. Technical differences among QUS systems are great, with different instruments using variable frequencies, different transducer sizes, and sometimes measuring different regions of interest, even at the same skeletal site. The calcaneus is the skeletal site most often tested, although other bones, including the radius, tibia, and finger phalanges, can be used. Commercial QUS systems usually measure two parameters- the speed of sound (SOS) and broadband ultrasound attenuation (BUA). A proprietary value, such as the “quantitative ultrasound index” (QUI) with the Hologic Sahara’ or “stiffness index” with the GE Healthcare Achilles Express, may be calculated from a combination of these measurements. SOS varies according to the type of bone, with a typical range of 3000-3600 meters per second (m/sec) with cortical bone and 1650-2300 m/sec for trabecular bone (22). A higher bone density is associated with a higher SOS. BUA, reported as decibels per megahertz (dB/MHz), is a measurement of the loss of energy, or attenuation, of the sound wave as it passes through bone. As with SOS, a higher bone density is associated with a higher BUA. Values obtained from calculations using ultrasound parameters may be used to generate an estimated BMD and a T-score. The T-score derived from a QUS measurement is not the same as a T-score from a DXA. QUS cannot be used for diagnostic classification and is not clinically useful to monitor the effects of therapy (23).

Quantitative computed tomography (QCT) and peripheral QCT (pQCT). QCT and pQCT measure trabecular and cortical volumetric BMD at the axial skeleton and peripheral skeletal sites, respectively. QCT is a useful research tool to enhance understanding of the pathophysiology of osteoporosis and the

mechanism of action of pharmacological agents used to treat osteoporosis. QCT predicts fracture risk, with the correlation varying according to skeletal site and bone compartment measured, type of fracture predicted, and population assessed (24). The ISCD Official Positions state that “spinal trabecular BMD as measured by QCT has at least the same ability to predict vertebral fractures as AP spinal BMD measured by central DXA in postmenopausal women with lack of sufficient evidence to support this position in men; pQCT of the forearm at the ultradistal radius predicts hip, but not spine, fragility fractures in postmenopausal women with lack of sufficient evidence to support this position in men (24). QCT is more expensive than DXA and QUS, uses higher levels of ionizing radiation, and cannot be used for diagnostic classification. T-scores by QCT are typically lower than with DXA (25), thereby overestimating the prevalence of osteoporosis when used incorrectly with the WHO diagnostic criteria.

WHO FRACTURE RISK ASSESSMENT TOOL (FRAX®)

The combination of BMD and CRFs predicts fracture risk better than BMD or CRFs alone (26,27). This has been recognized for many years (2), yet until recently, CRFs have played a relatively minor role compared with BMD in the assessment of fracture risk. In order to assist physicians in making a more accurate quantitative assessment of fracture risk, the WHO, in cooperation with other scientific societies (e.g., ISCD, NOF), has developed FRAX, a computer-based algorithm that estimates the 10-year probability of hip fracture and major osteoporotic fracture (i.e., clinical spine, hip, proximal humerus, and distal forearm fracture). FRAX can be accessed online at http://www.shef.ac.uk/FRAX (Figure 1), on some software versions of DXA systems, and on some handheld computer devices. FRAX is based on analysis of data from 12 large prospective observational studies in about 60,000 untreated men and women in different world regions, having over 250,000 person-years of observation and more than 5,000 reported fractures reported.

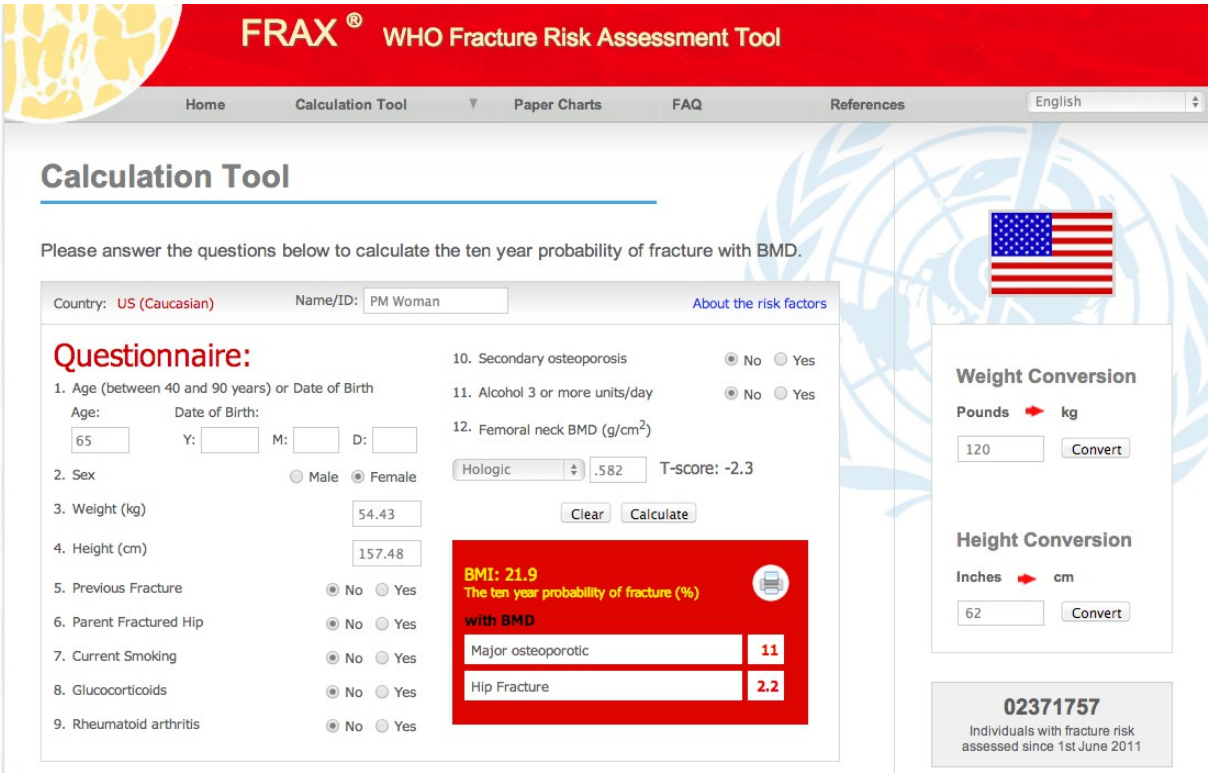

Figure 1. FRAX online for US Caucasian patients. This example shows a 65 year-old woman who has no clinical risk factors for fracture and a femoral neck T-score of -2.3 with a Hologic instrument. The 10-year probability of major osteoporotic fracture is 11% and the 10-year probability of hip fracture is 2.2%.

These levels do not meet the National Osteoporosis Foundation guidelines for initiation of pharmacological therapy in the US (7). Image reproduced with permission of the World Health Organization.

The input for FRAX is the patient's age, sex, height, weight, a "yes" or "no" response indicating the presence or absence for each of 7 CRFs: 1. previous 'spontaneous' or fragility fracture as an adult; 2. parent with hip fracture; 3. current tobacco smoking; 4. ever use of chronic glucocorticoids at least 5 mg prednisolone for at least 3 months; 5. confirmed rheumatoid arthritis; 6. secondary osteoporosis, such as type 1 diabetes, osteogenesis imperfecta in adults, untreated longstanding hypothyroidism and hypogonadism, or premature menopause (note: this is a "dummy" risk factor that has no effect on the fracture risk calculation unless no femoral neck BMD value is entered); 7. alcohol intake greater than 3 units per day, with a unit of alcohol defined as equivalent to a glass of beer, an ounce of spirits or a medium-sized glass of wine), and femoral neck BMD, if available. Since the introduction of FRAX, upgrades have been introduced to correct errors, enhance its usability, and incorporate new data that have become available.

Benefits of FRAX. The use of FRAX provides a quantitative estimation of fracture risk that is based on robust data in large populations of men and women with ethnic and geographic diversity. Expression of fracture risk as a probability provides greater clinical utility for than relative risk. When combined with cost-utility analysis, a fracture risk level at which it is cost-effective to treat may be derived. FRAX can be used to estimate fracture probability without femoral neck BMD, allowing it to be used when DXA in unavailable or inaccessible.

Limitations of FRAX. To generate a valid FRAX output, the responses to CRF questions must be correct; for example, an incorrect entry of self-reported rheumatoid arthritis or use of glucocorticoids could skew the results toward overestimation of fracture risk. FRAX may underestimate or overestimate fracture risk due to dichotomized (yes or no) input for CRFs that in reality are associated with a range of risk that varies according to dose, duration of exposure, or severity; for example, fracture risk may be underestimated when a patient is on high-dose glucocorticoid therapy or has had multiple recent fragility fractures, even when a "yes" response is entered for these CRFs. FRAX is validated only in untreated patients and may overestimate fracture risk when the patient is being treated; the NOF/ISCD guidance on FRAX suggests that "untreated" may be interpreted as never treated or if previously treated, no bisphosphonate for the past 2 years (unless it is an oral agent taken for less than 2 months); and no estrogen, raloxifene, calcitonin, or denosumab for the past 1 year (7). In this context, calcium and vitamin D do not constitute treatment. FRAX in the US allows input for 4 ethnicities (Caucasian, Black, Hispanic, Asia); it is not clear how to use FRAX for patients of other ethnicities or a mix of these ethnicities. Answering "yes" for the category of secondary osteoporosis has no effect on the fracture risk calculation as long as a value for femoral neck BMD is entered. The range of error for a fracture probability generated by FRAX is unknown, but may be substantial in some cases. Some important risk factors, such as falls and frailty, are not directly entered into FRAX, although they are indirectly included insofar as they are a component of aging. FRAX may underestimate fracture risk when the lumbar spine BMD is substantially lower than femoral neck BMD, as may occur in about 15% of patients (28).

Despite the numerous limitations of FRAX, it is a helpful clinical tool when used with a good understanding of factors that may result in underestimation or overestimation of fracture risk. FRAX may enhance discussion of risk with the patient and help to identify those who are at sufficiently high for fracture to benefit from therapy.

MEDICAL HISTORY

A thorough medical history may identify risk factors for osteoporosis and fractures, suggesting that a bone density test and/or further evaluation is indicated. The medical history may also reveal symptoms of potentially correctable causes of skeletal fragility (e.g., gluten intolerance with celiac disease) or co-morbidities that could influence treatment decisions (e.g., esophageal stricture suggests that oral bisphosphonates should not be given). A history of falls is a predictor of future falls, with that risk potentially modifiable though appropriate interventions. Finally, some symptoms may trigger further

evaluation for the presence of fractures (e.g., historical height loss or development of kyphotic posture suggests the possibility of vertebral fractures that may warrant spine imaging). Table 7 provides examples of helpful information that might be obtained from a thoughtful interactive discussion with the patient.

Medical history for patients with osteoporosis. A thorough review of systems and history of relevant familial disorders, previous surgical procedures, medications, dietary supplements, food intolerances and lifestyle provide helpful information in the management of patients with osteoporosis. Such historical information may play a role in determining who should have a bone density test, assessing fracture risk, providing input for the World Health Organization fracture risk assessment tool (FRAX®), evaluating for secondary causes of osteoporosis, selecting the most appropriate treatment to reduce fracture risk, and finding factors contributing to suboptimal response to therapy. Listed here are key components of the skeletal health history and examples of the potential impact on patient care.

Table 7

Clinical Utility	**Medical History**
Assist in determining who need a bone density test	See Table 3
Assessing fracture risk	See Table 3 and 4
Input for FRAX®	Age, sex, weight, height, previous fracture, parent with hip fracture, current tobacco smoking, ever use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol intake 3 or more units per day, and femoral neck bone mineral density (if available)
Evaluating for secondary causes of osteoporosis	See Tab le 3
Selecting most appropriate treatment	Identify co-morbidities of clinical significance. For example, high risk of breast cancer favors raloxifene use, while history of thrombophlebitis suggests that raloxifene should not be used; esophageal stricture is a contraindication for oral bisphosphonate use; a patient with a skeletal malignancy should not be treated with teriparatide.
Factors contributing to suboptimal response to therapy	Compliance and persistence to therapy; adequacy of calcium and vitamin D; comorbidities listed in Table3.

PHYSICAL EXAM

Findings of importance on the physical exam of a patient with osteoporosis may be the sequelae of old fractures (e.g., kyphosis due to old vertebral fractures), a consequence of a recent fracture (e.g., localized vertebral spinous process tenderness with a new vertebral fracture), or abnormalities suggestive of a secondary cause of osteoporosis (e.g., thyromegaly with thyrotoxicosis). An accurate measurement of height with a wall-mounted stadiometer is a helpful office tool for evaluating patients at risk for fracture. A height loss of 1.5 inches (4.0 cm) or more compared to the historical maximum (29,30) or a loss of 0.75 inches (2.0 cm) or more compared to a previous measured height (31) suggests a high likelihood of vertebral fracture. Body weight measurement is part of the osteoporosis evaluation because low body weight (less than 127 lbs) (32), low BMI (20 kg/m^2 or less) (33), and weight loss of 5% or more (34) are associated with increased risk of fracture. Localized tenderness of the spine, kyphosis, or diminished distance between the lower ribs and the pelvic brim may be the result of one or more vertebral fractures. Abnormalities of gait, posture, balance, muscle strength, or the presence of postural hypotension or impaired level of consciousness may be associated with increased risk of falling. Bone tenderness may be the caused by osteomalacia. Atrophic testicles suggest hypogonadism. Patients should be observed for stigmata of hyperthyroidism or Cushing's syndrome. Blue sclera, hearing loss, and yellow-brown teeth are suggestive of osteogenesis imperfecta. Joint hypermobility and skin fragility could be due to Ehlers-Danlos syndrome. Urticaria pigmentosa may occur with systemic mastocytosis. Table 8 shows examples of abnormal physical exam findings with osteoporosis.

Table 8. Focused physical examination in patient with osteoporosis. This table provides examples of findings on physical exam that may be helpful in the evaluation of skeletal health. It is not intended to show all findings of importance.

Component of physical exam	Example of finding of potential skeletal importance	Potential clinical implications for skeletal health
Vital signs	Low body weight or body mass index	Anorexia nervosa
	Loss of height	Vertebral fracture
	Loss of weight	Malignancy, malabsorption
Skin	Urticaria pigmentosa	Systemic mastocytosis
	Striae, acne	Cushing's syndrome, exogenous glucocorticoids
Head	Cranial dysostosis	Hypophosphatasia
Eyes	Blue sclera	Osteogenesis imperfecta
Ears	Hearing loss	Osteogenesis imperfecta, sclerosteosis

Nose	Anosmia	Kallmann syndrome
Throat	Poor dentition	Increased risk of osteonecrosis of the jaw
Neck	Thyromegaly	Thyrotoxicosis
Lungs	Decreased breath sounds	Chronic obstructive pulmonary disease
Heart	Aortic insufficiency	Marfan’s syndrome
Musculoskeletal	Kyphosis	Vertebral fractures
	Spinous process tenderness	Acute vertebral fracture
	Decreased space between lower ribs and pelvis	Vertebral fractures
	Tender bones	Osteomalacia
	Inflammatory joint disease	Rheumatoid arthritis
	Hypermobility of joints	Ehlers-Danlos syndrome
	Muscle weakness	Vitamin D deficiency, osteomalacia
Abdomen	Hepatomegaly	Chronic liver disease
	Surgical scars	Bariatric surgery, gastrectomy
Genitalia	Testicular atrophy	Hypogonadism
Neurological	Poor balance	High fall risk, vitamin D deficiency
	Dementia	Poor adherence to therapy, high fall risk

EVALUATION FOR SECONDARY CAUSES OF OSTEOPOROSIS

The possibility of previously unrecognized causes of skeletal fragility should be considered in every patient with osteoporosis (35). After an initial medical history is taken and physical exam is performed, appropriate laboratory testing and imaging may provide information that is critical for ongoing patient care. Osteoporosis is commonly divided into two categories according to etiology. "Primary osteoporosis" is due to time-appropriate postmenopausal estrogen deficiency (type I osteoporosis, preferentially involving trabecular bone loss) or to aging in men and women (type II osteoporosis, with a combination of trabecular and cortical bone loss). 'secondary osteoporosis' is caused by other conditions, diseases, or medications, with or without the presence of primary osteoporosis.

The reported prevalence of secondary osteoporosis varies depending on the study population, the extent of the medical evaluation, and definitions for laboratory abnormalities. It is likely that many or most patients with primary osteoporosis have clinically significant contributing factors that may influence patient management. In a study of North American women receiving osteoporosis therapy, it was found that 52% had vitamin D inadequacy, defined as serum 25-hydroxyvitamin D (25-OH-D) levels less than 30 ng/ml (36). In another study of patients referred to an osteoporosis clinic, over 60% were found to have elements of secondary osteoporosis when vitamin D deficiency was very conservatively defined as serum 25-OH-D level less than 12.5 ng/ml (37,38). In the same study, the number of patients with secondary osteoporosis was much higher when vitamin D inadequacy was more appropriately defined as serum 25-OH-D less than 33 ng/ml (39,40).

It has been proposed by some that a bone density that is less than expected compared to an age- and sex-matched population, as represented by a low Z-score (e.g., less than -2.0), suggests a high likelihood of secondary osteoporosis and should be one of the triggers for further investigation (41,42). While there may be some merit to this concept, there are few if any studies validating the use of a Z-score cutoff for this purpose. Since secondary osteoporosis is common, a more effective strategy is to screen all patients with osteoporosis for contributing factors (43). The results of a metabolic evaluation may identify previously unrecognized diseases and conditions that require treatment in addition to, or instead of, standard osteoporosis pharmacological therapy.

Depending on the patient population being studied, different causes of secondary osteoporosis may predominate. Calcium deficiency, vitamin D deficiency, and sedentary lifestyle are common contributing factors for all patients. In women referred to an osteoporosis clinic with previously recognized medications or diseases contributing to osteoporosis, the most common were history of glucocorticoid use (36%), premature ovarian failure (21%), history of unintentional weight loss (10%), history of alcoholism (10%), and history of liver disease (10%) (37). When patients without previously recognized contributing factors were evaluated at the same specialty clinic, most were 55% were found to have vitamin D deficiency or insufficiency (serum 25-OH-D less than 33 ng/ml) (40), while 10% had hypercalciuria, 8% had malabsorption, and 7% had primary or secondary hyperparathyroidism (37). In men, the most common secondary causes of osteoporosis are long-term glucocorticoid use, hypogonadism, and alcoholism (44,45). The increasing use of aromatase inhibitor therapy for breast cancer in women (46) and androgen deprivation therapy for prostate cancer in men (47) is now recognized as an important factor in the development of osteoporosis in these patients. Other common causes for low BMD and fractures include multiple myeloma (48), gastric bypass surgery (49) and gastric resection (50). Treatable but easily missed secondary causes of osteoporosis include asymptomatic primary hyperparathyroidism (51), subclinical hyperthyroidism (52), mild Cushing's syndrome (53), and malabsorption due to unrecognized celiac disease (54). Table 9lists some of the causes of low BMD by category.

Table 9. Many causes of low bone mineral density.

Inherited	Nutritional	Endocrine	Drugs	Other

Osteogenesis imperfecta	Malabsorption	Hypogonadism	Glucocorticoids	Multiple myeloma
Homocystinuria	Chronic liver disease	Hyperthyroidism	Anticonvulsants	Rheumatoid arthritis
Marfan's syndrome	Alcoholism	Hyperparathyroidism	Long-term heparin	Systemic mastocytosis
Hypophosphatasia	Calcium deficient diet	Cushing's syndrome	Excess thyroid	Immobilization
	Vitamin D deficiency	Eating disorder	GnRH agonists	
			Aromatase inhibitors	

A variety of testing strategies have been proposed as screening for all patients with osteoporosis (35,37,40,43,55,56). A minimal cost-effective work-up for all patients consists of a complete blood count (CBC), serum calcium, phosphorus, creatinine with calculated or measured creatinine clearance, alkaline phosphatase, 24-hour urinary calcium, and serum 25-OH-D. Other laboratory tests may be indicated according to the patient's clinical profile and the practice setting. A summary of useful common and uncommon laboratory studies with comments on their possible skeletal significance is provided below.

CLINICAL CASE

A 52-year postmenopausal woman with a history of irritable bowel syndrome (IBS) and a family history of osteoporosis (mother with hip fracture) is found to have osteoporosis on a DXA study. Evaluation for secondary causes of osteoporosis is unremarkable except for mild iron deficiency anemia (a long-standing problem, previously attributed to heavy menses) and a low 24-hour urinary calcium of 30 mg, with adequate calcium intake and normal renal function. Serum 25-OH-D is 29 ng/ml. Additional work-up shows a high titer of IgA endomysial antibodies consistent with celiac disease. This diagnosis is confirmed by a small bowel biopsy showing villous atrophy. She is started on a gluten-free diet, resulting in resolution of her "IBS" symptoms and correction of her anemia. One year later, with no pharmacological therapy for osteoporosis, there is a statistically significant BMD increase of 9% at the lumbar spine.

Celiac disease may result in osteoporosis due to calcium malabsorption, even in the absence of gastrointestinal symptoms. Treatment is strict lifelong adherence to a gluten-free diet, which may sometimes be followed by a substantial increase in BMD, as seen in this patient. A 24-hour urinary calcium is an inexpensive screening test for calcium malabsorption that should be considered a routine part of the initial evaluation of osteoporosis.

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BASIC BLOOD TESTS

CBC- Anemia may be seen in patients with multiple myeloma or malnutrition.
Sedimentation rate- May be elevated with multiple myeloma.
Calcium- Among the many causes of hypercalcemia are primary and secondary hyperparathyroidism, hyperthyroidism, renal failure, vitamin D intoxication, and Paget's disease. Hypocalcemia may be seen with vitamin D deficiency and hyperphosphatemia.
Phosphorus- Hyperphosphatemia may occur with hypoparathyroidism, renal failure, and possibly with bisphosphonate therapy. Hypophosphatemia may be seen with primary or secondary hyperparathyroidism, vitamin D deficiency, and oncogenic osteomalacia.
Alkaline phosphatase- High values can be seen with healing fractures, osteomalacia, and Paget's disease, as well as occurring normally in growing children. Low values occur with hypophosphatasia, a rare genetic disorder that causes impaired mineralization of bone and dental tissue.
Vitamin D- The test that best reflects vitamin D stores is the serum 25-OH-D. While there is no consensus on the optimal range of serum 25-OH-D, a reasonable target for good skeletal health is approximately 30-60 ng/ml. This is likely to maximize intestinal absorption of calcium and minimize serum PTH levels. Interpretation of serum 25-OH-D levels is confounded by assay variability (57). Serum 1,25-(OH)2-D is usually not helpful in the evaluation of osteoporosis patients, unless there are concerns regarding renal conversion of 25-OH-D to 1,25(OH)2-D. Deficiency or insufficiency of vitamin D is very common and play a role in the pathogenesis of osteoporosis and osteomalacia.
Creatinine- Chronic kidney disease may cause an elevated creatinine level and renal osteodystrophy. Elderly patients with small muscle mass may have impaired renal function with a "normal" serum creatinine. An estimated glomerular filtration rate can be calculated using one of many formulae, such as that of Cockcroft and Gault (58) or modification of diet in renal disease study equation (59). Impaired renal function not only has adverse skeletal effects but also raises considerations regarding the type and dose of pharmacologic agents used.
TSH- Hyperthyroidism from any cause, including excess thyroid replacement, can usually be recognized by a low TSH. High bone turnover associated hyperthyroidism is associated with loss of bone mass.
Liver enzymes- Abnormalities may be caused by chronic liver disease, which is a risk factor for osteoporosis.

BASIC URINE TESTS

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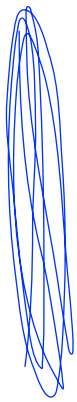
Urinalysis. Proteinuria may occur with multiple myeloma or chronic kidney disease. Abnormal cells may suggest kidney disease.

24-hour urine for calcium- A well-collected 24-hour urine for calcium is a helpful screening test for identifying patients with common disorders of calcium metabolism. The "normal" range of urinary calcium is not well established, and varies according to many dietary factors and estrogen status in women (60,61). As a "rule of thumb," urinary calcium may be considered elevated when it is greater than 250 mg per 24 hours in women; greater than 300 mg per 24 hours in men; or greater than 4 mg/kg body weight per 24 hours in either sex. It has been proposed that hypercalciuria can be easily classified as "renal" (renal calcium leak), "resorptive" (excess skeletal loss of calcium) or "absorptive" (increased intestinal absorption of calcium) (62). However, in clinical practice, these distinctions are not so easily established. Idiopathic hypercalciuria, perhaps the most common type of hypercalciuria (63), may be diagnosed if there are no underlying medical disorders (e.g., hyperparathyroidism, vitamin D toxicity, Paget's disease of bone, multiple myeloma, sarcoidosis) and no obvious dietary excesses (e.g., calcium, sodium, protein, carbohydrates, alcohol) or deficiencies (e.g., phosphate, potassium) that are associated with hypercalciuria (61). In the absence of dietary calcium deficiency, vitamin D deficiency, malabsorption, liver disease, or chronic renal failure, low urinary calcium (less than 50 mg per 24 hours in women or men) is suggestive of calcium malabsorption and warrants further investigation. Celiac disease is a common (64) cause of asymptomatic malabsorption in osteoporosis that is treatable with a gluten-free diet (54).



Additional Studies in Selected Patients

Celiac antibodies- Anti-endomysial antibody and tissue transglutaminase antibody are currently the serological markers of choice, with a higher sensitivity and specificity than anti-gliadin antibody and

antireticulin antibody (65). If a serological marker is abnormal, or if there is a high clinical suspicion for celiac disease, the patient should be referred for endoscopy and small bowel biopsy.

Intact PTH- This may be elevated in patients with primary hyperparathyroidism, vitamin D deficiency, or renal failure.

Serum and urine protein electrophoresis- These are helpful tests to screen for possible multiple myeloma. If an M-component is identified, referral for bone marrow aspiration may be indicated.

Dexamethasone suppression test or 24-hour urinary free cortisol- This is helpful to evaluate patients with suspected Cushing's syndrome.

Serum total or free testosterone level- A useful test for all men with osteoporosis.

Serum homocysteine- Elevated circulating homocysteine levels are associated with increased risk of fracture (66,67). It is not know whether reduction of homocysteine levels by increasing dietary intake of folic acid and vitamins B6 and B12 reduces the risk of fracture.

Serum tryptase and 24-hour urine for N-methylhistamine- Systemic mastocytosis is a rare cause of osteoporosis that can be diagnosed by a biopsy of typical skin lesions of urticaria pigmentosa, when present. Patients with systemic mastocytosis may sometimes present with osteoporosis and no other manifestations of the disease (68,69). When this disorder is suspected but skin lesions are not present, the finding of an elevated serum typtase and/or urinary N-methyl histamine can be helpful, especially during or soon after a symptomatic episode of histamine release. However, normal values do not exclude the diagnosis. Bone marrow aspiration or biopsy, or non-decalcified double tetracycline labeled transiliac bone biopsy, may be necessary to confirm the diagnosis.

Serum bicarbonate- Renal tubular acidosis (RTA) has been associated with osteoporosis (70). With distal (type I) RTA, the serum bicarbonate is usually less than 15 mmol/l with a urine pH greater than 5.5.

BONE TURNOVER MARKERS

Bone turnover markers (BTMs) are noninvasive laboratory tests of serum and urine that are readily available in clinical practice. While BTMs cannot be used to diagnose osteoporosis or determine the cause to osteoporosis, they have been very helpful in the research to understand the pathophysiology of osteoporosis and other skeletal diseases and the mechanism of action of interventions used in the treatment of osteoporosis. In clinical practice, BTMs offer the potential of predicting fracture risk independently of BMD and may be useful in monitoring the metabolic effects of therapy (71). Drugs that are approved for the management of osteoporosis modulate bone remodeling in ways that are reflected by changes in BTMs. A decrease in BTMs with antiresorptive therapy is predictive of a subsequent increase in BMD (72) and reduction in fracture risk (73-76). The magnitude of BTM decrease with antiresorptive therapy is significantly associated with the level of fracture risk reduction, although the proportion of treatment effect due to the reduction in BTMs appears to vary according to the type of drug used (77). With teriparatide, a bone anabolic agent, an early increase in BTM levels is predictive of a subsequent increase in BMD (78).

Markers of bone resorption are mostly fragments of type I collagen, the main component of the organic bone matrix, that are released during osteoclastic bone resorption. These are measured in the serum or urine, with those available for clinical use including N-telopeptide of type I collagen (NTX), C-telopeptide of type I collagen (CTX), deoxypyridinoline (DPD), and pyridinoline (PYD). Bone formation markers are proteins secreted by osteoblasts or byproducts of type I collagen production by osteoblasts. They are measured in the serum and include bone specific alkaline phosphatase (BSAP), N-terminal propeptide of type I collagen (P1NP), and osteocalcin.

Clinical use of BTMs requires knowledge of their limitations as well as benefits. BTMs are subject to pre-analytical (biological) and analytical variability. Uncontrollable sources of pre-analytical variability include

age, sex, menopausal status, pregnancy, lactation, fractures, co-existing diseases (e.g., diabetes mellitus, impaired renal function, and liver disease), drugs (e.g., glucocorticoids, anticonvulsants, and gonadotropin hormone releasing agonists) and immobility (79). Controllable pre-analytical sources of variability include time of day (circadian variability), fasting status, and exercise (79). Analytical sources of variability include specimen processing (e.g., collection, handling, and storage) (80). Between-laboratory variability may be large (reported to be as much as a 7.3-fold difference), casting doubt on the validity of comparing specimens sent to different labs (81). Reference ranges for BTMs are not well established and may vary according to the population tested, the type of BTM, and the circumstances under which it is collected and processed.

In order to compare BTMs measurements longitudinally, it would be ideal to know the LSC and use this in a manner similar to what should be (but is probably not) common practice with DXA. However, the standards for calculating an LSC for a BTM are not as clear as with DXA, and the opportunity to do precision assessment for a BTM may not present itself. The NOF recommends calculating the LSC with a 95% level of confidence for each BTM used by multiplying the laboratory-provided precision error by 2.77 (82). The NOF also recommends that specimens be obtained in the early morning following an overnight fast to reduce biological variability, with serial measurements to be obtained at the same time of day and ideally during the same season of the year. The Belgian Bone Club suggests using an estimated LSC of assuming an LSC of about 30% for serum BTMs and about 50-60% for urine BTMs (71). While the LSC for BTMs is almost always greater than for DXA, the magnitude of likely change (83) is greater than DXA, with the 'signal to noise ratio' that may be as good or even better than DXA.

Evidence-based guidelines for the clinical use of BTMs have been developed by organizations that include the NOF (7), Belgian Bone Club (71), and the Japan Osteoporosis Society (84). The NOF guidelines state that "suppression of biochemical markers of bone turnover after 3-6 months of specific antiresorptive osteoporosis therapies, and biochemical marker increases after 1-3 months of specific anabolic therapies, have been predictive of greater BMD responses and in some cases fracture risk reduction in large clinical trials. Biochemical marker changes in individuals must exceed the LSC in order to be clinically meaningful." The Belgian Bone Club suggests that "early changes in BTM can be used to measure the clinical efficacy of an antiresorptive treatment and to reinforce patient compliance," with goal of decreasing the BTM to the premenopausal range or at least achieving a decrease as great as the LSC. The Japanese guidelines indicate that "the argument for measuring bone turnover markers to evaluate the therapeutic effects of bone antiresorptive medications can be justified," but go on to state that there is insufficient evidence for their use with medications having other mechanisms of action (84).

A significant change of a BTM level in the appropriate direction following therapy is evidence that the patient is taking the drug regularly, taking it correctly, and that it is being absorbed and having the expected effect in modulating bone remodeling. Failure to achieve such a change in the BTM level is cause for concern and suggests that evaluation and possibly a reconsideration of treatment should be considered (85). The use of BTMs allows assessment of drug effect sooner than with DXA, so that evaluation and corrective action, if needed, can be taken early in the course of therapy rather than later. Monitoring BTMs, especially in association with regular contact by a healthcare provider, may improve persistence with therapy (86). Despite the well-described limitations of BTMs (87), there is emerging support for their use in clinical practice, particularly in the assessment of response to therapy (88,89). Clinicians who are familiar with the benefits and limitations of BTMs may find them a helpful tool, in association with BMD testing, for managing patients with osteoporosis.

IMAGING STUDIES

Standard X-rays are used to diagnose fractures of all types and may sometimes suggest secondary causes of osteoporosis. Pseudofractures (Looser's zones) are radiolucent lines running perpendicular to the bone cortex that may be seen in patients with osteomalacia. These probably represent stress fractures that have healed with poorly mineralized osteoid. Punctate radiolucencies may be seen in bone X-rays of patients with systemic mastocytosis. Primary hyperparathyroidism may cause bone cysts, subperiosteal bone resorption, brown tumors, and demineralization ('salt and pepper' pattern) of the

skull. MRI, CT scanning, or nuclear imaging may be used to detect stress fractures not visible on X-ray. MRI of the spine is commonly used prior to vertebroplasty or kyphoplasty to determine the age of the fracture, the likelihood of the fracture being from causes other than osteoporosis, and whether there is retropulsion of bony fragments than could impair neurological function.

BONE BIOPSY

Non-decalcified double tetracycline labeled iliac crest bone biopsy is rarely used in clinical practice, but may be helpful with difficult diagnostic problems. In the evaluation of renal osteodystrophy, a bone biopsy can distinguish between high turnover and low turnover bone disease, and possibly be an aid in the selection of therapy. With infiltrative disorders of bone, such as systemic mastocytosis, a bone biopsy or bone marrow aspiration may sometimes be the only way to make the diagnosis. In patients who are not responding to therapy as expected, or in patients with unusual presentations of osteoporosis, a bone biopsy may be indicated. Bone biopsies are required by the FDA for safety monitoring in clinical trials of osteoporosis drugs.

SUMMARY

Osteoporosis is a common skeletal disease with serious clinical consequences. Effective management of skeletal health includes appropriate selection of patients for bone density testing and assessment of risk factors for fracture. Prior to treatment, and when response to treatment is suboptimal, patients should be evaluated for secondary causes of osteoporosis. All reversible factors should be corrected and treatment should be individualized based on the clinical circumstances.

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