Current Concepts Review

The Assessment of Fracture Risk

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- Bone mineral density is considered to be the standard measure for the diagnosis of osteoporosis and the assessment of fracture risk. The majority of fragility fractures occur in patients with bone mineral density in the osteopenic range.
- The Fracture Risk Assessment Tool (FRAX) can be used as an assessment modality for the prediction of fractures on the basis of clinical risk factors, with or without the use of femoral neck bone mineral density. Treatment of osteoporosis should be considered for patients with low bone mineral density (a T-score of between −1.0 and −2.5) as well as a ten-year risk of hip fracture of ≥3% or a ten-year risk of a major osteoporosis-related fracture of ≥20% as assessed with the FRAX.
- Biochemical bone markers are useful for monitoring the efficacy of antiresorptive or anabolic therapy and may aid in identifying patients who have a high risk of fracture.
- An approach combining the assessment of bone mineral density, clinical risk factors for fracture with use of the FRAX, and bone turnover markers will improve the prediction of fracture risk and enhance the evaluation of patients with osteoporosis.

Osteoporosis is the most common metabolic bone disease, and it affects up to 40% of postmenopausal women[1]. It is considered a silent disease because bone loss occurs without symptoms or signs, and approximately two-thirds of vertebral fractures are asymptomatic[2]. Osteoporosis with fractures frequently goes unrecognized in the clinical setting. Although it is important to initiate osteoporosis treatment following a fragility fracture (a low-energy fracture resulting from a fall from no greater than a standing height), several studies on the treatment of osteoporosis following hip fractures have demonstrated that osteoporosis treatment rates were actually low, ranging from 5% to 30%[3-8]. Therefore, the goal in evaluating patients is to identify those who are at risk for an osteoporotic fracture and to prevent future fractures once a fragility fracture has been diagnosed.

The National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy defines osteoporosis as a skeletal disorder characterized by low bone strength and increased risk of fracture[9]. This definition of osteoporosis reflects the changing perspective on this disease—i.e., osteoporosis is no longer considered a disorder of low bone mineral density alone. Epidemiologic studies have been performed to examine the risk factors that are associated with low bone mineral density and hip fractures[10,11]. As outlined by the National Osteoporosis Foundation, major risk factors for osteoporosis and related fractures include a personal history of fracture as an adult, a history of a fragility fracture in a first-degree relative (parent, sibling, or offspring), low body weight, current smoking, and use of oral corticosteroid therapy[12]. Risk factors for hip fracture were examined by the Study of Osteoporotic Fractures Research Group, which followed 9704 postmenopausal women who were sixty-five years of age or older[13]. The investigators determined that many factors, in addition to low bone mineral density, contribute independently to the risk of fracture, including age, history of maternal hip fracture, low body weight, height, poor health, previous hyperthyroidism, poor depth perception, tachycardia, previous fracture, and benzodiazepine use. Although clinicians may use this information as a rough guide for each individual, there is a need for a systemic approach to fracture risk assessment.

This present article will focus on factors that contribute to bone strength. We review the parameters and methods used

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to assess fracture risk, which include bone mineral density as assessed with dual x-ray absorptiometry, the Fracture Risk Assessment Tool (FRAX), bone turnover, and biochemical bone markers.

Assessment of Bone Quantity: Bone Mineral Density

In 1994, the World Health Organization developed a definition of osteoporosis on the basis of studies of women of various ages[14]. Bone mineral density, measured with dual x-ray absorptiometry, is expressed in absolute terms as grams of mineral per square centimeter scanned (g/cm^2). A patient's bone mineral density can also be related to a reference value for young normal adults of the same sex by using the T-score. The T-score is reported as the number of standard deviations that a patient's bone mineral density value is above or below the reference value for a healthy thirty-year-old adult. This definition became widely used, and osteoporosis was subsequently defined by the standard deviation rather than by an absolute value of bone mineral density. The World Health Organization T-score cut-off value for osteoporosis is −2.5. Fracture risk increases approximately twofold for every standard deviation below the mean for a young adult[15,16]. Therefore, low bone mineral density remains a strong predictor of future fracture risk.

Although measurement of bone mineral density with dual x-ray absorptiometry is the so-called gold standard for diagnosis of osteoporosis, it has some limitations. First, dual x-ray absorptiometry provides a two-dimensional projection of a three-dimensional structure and cannot capture three-dimensional bone geometry or microarchitecture. Thus, the bone mineral density values obtained with dual x-ray absorptiometry do not represent true volumetric bone mineral density but rather a projected areal bone mineral density. Bone mineral density determined with dual x-ray absorptiometry is confounded by bone size because dual x-ray absorptiometry cannot distinguish between increased bone mineral density values arising from thicker bones (geometric change) and those arising from increased tissue mineral density (material change). In addition, the scans used clinically can also be distorted by aortic calcification, soft-tissue calcification, and other artifacts in an older individual at greater risk for fracture. Finally, bone mineral density provides static information. Changes in bone mineral density occur slowly, and one may not be able to detect any differences several years after osteoporosis treatment[17-19].

Bone mineral density cannot be used as the sole predictor of bone strength; <50% of the variation in whole-bone strength is attributable to variations in bone mineral density[20-23]. In fact, the majority of patients who sustain fragility fractures have a T-score above −2.5[24-26]. The National Osteoporosis Risk Assessment study revealed that 82% (1852) of 2259 postmenopausal women with a fracture after one year of follow-up had a T-score above −2.5 and 67% (1514) had a T-score of greater than −2.0 as measured with peripheral densitometry[24]. Similarly, in a Rotterdam study of 7806 individuals fifty-five years of age or older, 56% (280 of 499) of the nonvertebral fractures in the women and 79% (115 of 145) in the men were in individuals with a T-score in the osteopenic range (between −1.0 and −2.5)[25].

Analyses of data from trials of antiresorptive drugs have shown that an improvement in spinal bone mineral density during treatment with such agents accounted for only a small part of the observed reduction in the risk of vertebral fracture[21,27]. For example, an analysis of the Fracture Intervention Trial data with use of logistic models of individual patient data revealed that an improvement in spinal bone mineral density contributed only 16% (95% confidence interval = 11% to 27%) of the achieved reduction in the risk of vertebral fracture during treatment with antiresorptive drugs[21]. An analysis of data on 2407 patients who received risedronate as compared with 1177 patients in a placebo group indicated that increases in bone mineral density in the lumbar spine explained only 18% (95% confidence interval = 10% to 26%) of the drug's efficacy with regard to the prevention of vertebral fracture[28]. This information suggests that factors other than bone mineral density contribute to a patient's risk of fracture.

Assessment of Fracture Risk by Using the Fracture Risk Assessment Tool (FRAX)

Several clinical factors are associated with a fracture risk that is greater than what can be accounted for by bone mineral density alone[29]. Fracture risk assessment, therefore, should employ specific risk factors in addition to bone mineral density. For example, age is a powerful independent risk factor that has largely been ignored in previous clinical guidelines. In women with a T-score of −2.5, the probability of hip fracture is five times greater at the age of eighty years than it is at the age of fifty years[30]. Thus, fracture risk can be assessed more accurately by considering both age and bone mineral density than it can by considering bone mineral density alone. Similarly, other clinical risk factors contribute independently to fracture risk[31] (Fig. 1).

FRAX Model

Because of the limitations of dual x-ray absorptiometry, efforts have been made to formulate a system to better predict fracture risk. On the basis of a series of meta-analyses undertaken to identify clinical risk factors for osteoporosis, the Fracture Risk Assessment Tool (FRAX) was developed[32-34]. FRAX, released in 2008 by the World Health Organization, was developed and validated under the direction of Professor John Kanis with the support of many individuals and organizations including the American Society for Bone and Mineral Research, the National Osteoporosis Foundation, the International Society for Clinical Densitometry, and the International Osteoporosis Foundation. FRAX is currently available online at www.shef.ac.uk/FRAX[32,35] (Fig. 2).

The aim of FRAX is to provide an assessment tool for the prediction of fractures in men and women with use of clinical risk factors with or without femoral neck bone mineral density. These clinical risk factors include age, sex, race, height, weight, body mass index, a history of fragility fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteopo-

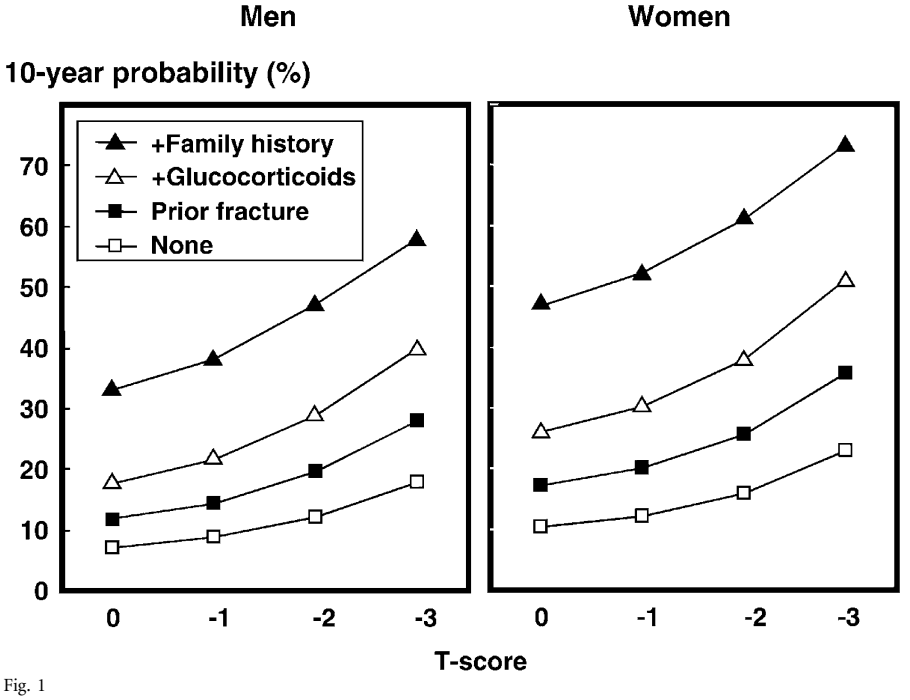

Fig. 1

The effects of several clinical risk factors on the ten-year probability of a major osteoporotic fracture occurring in sixty-five-year-old white men and women from the United States[31]. (Reprinted from: Kanis JA, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX® and its applications to clinical practice. Bone. 2009;44:734-43, with permission from Elsevier.)

rosis, current smoking, and alcohol intake of three or more units daily (Table I). FRAX calculates the ten-year probability of a major osteoporotic fracture (in the proximal part of the humerus, the wrist, or the hip or a clinical vertebral fracture) and of a hip fracture calibrated to the fracture and death hazards[30,36]. The initial FRAX model required a T-score calculated by means of a so-called FRAX patch[37]; however, in February 2009, FRAX was revised so that clinicians could either enter T-scores or select the manufacturer of the densitometry equipment (such as Hologic, GE Lunar, or Norland) and enter the femoral neck bone mineral density in grams per square centimeter.

In addition to the clinical risk factors, the geographic area in which each individual resides should be considered in the fracture risk assessment. Fracture probability varies markedly among different regions of the world[38]. FRAX allows fracture risk to be calculated for countries where the incidences of both fractures and mortality are known. Currently, a FRAX model is available for Austria, China, Germany, France, Italy, Japan, Spain, Sweden, Switzerland, Turkey, the United Kingdom, the United States, Argentina, Belgium, Finland, Hong Kong, Lebanon, and New Zealand. In a country where there is no FRAX model, a representative surrogate country should be chosen[31].

Clinical Guidelines

The application of FRAX includes selecting an appropriate group of patients for osteoporosis treatment. In the United States, the National Osteoporosis Foundation recommends using FRAX to calculate fracture risk for patients who have T-scores between −1.0 and −2.5 in the spine, femoral neck, or total hip region. FRAX should not be used for patients who have already received pharmacologic treatment for osteoporosis. The 2008 National Osteoporosis Foundation recommendations for pharmacologic treatment of osteoporosis (Table II) are based in part on the U.S. adaptations of the World Health Organization ten-year fracture probability model and algorithms for determining treatment thresholds[39]. These recommendations are based on cost-effectiveness in populations of patients and should be used together with other considerations when making treatment decisions for individual patients.

According to the 2008 National Osteoporosis Foundation recommendations, treatment of osteoporosis should be considered for (1) patients with a history of hip or vertebral fracture, (2) patients with a T-score of −2.5 or lower at the femoral neck or spine, and (3) patients who have a T-score of between −1.0 and −2.5 at the femoral neck or spine and a ten-year hip fracture risk of ≥3% or a ten-year risk of a major osteoporosis-related fracture of ≥20% as assessed with the FRAX[39,40]. The advantages of this new recommendation as compared with the 2003 National Osteoporosis Foundation recommendations include better allocation of limited healthcare resources to patients who are at higher risk for fracture and most likely to benefit from therapy. In addition, these new guidelines take into consideration different ethnicities in the United States and include the male population[41].

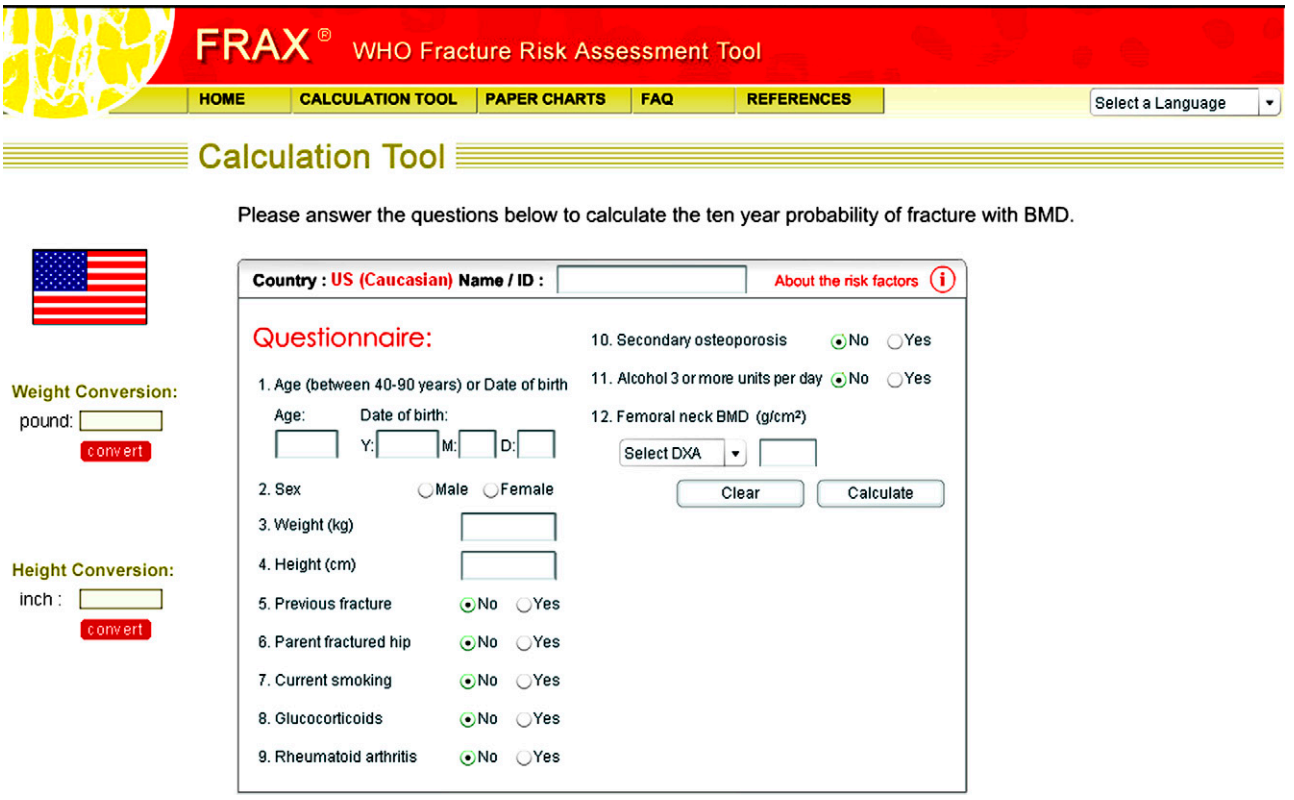

Fig. 2

Image of FRAX® web page (http://www.shef.ac.uk/FRAX) showing the chart for input of data and format of results in the United States version of the FRAX® tool. (Printed with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield. FRAX® is registered to Professor J.A. Kanis, University of Sheffield.)

Osteoporosis treatment is cost-effective for patients with a history of a fragility fracture and those with osteoporosis according to the World Health Organization criterion (a T-score of −2.5 or less), as demonstrated in a study of the financial implications of the new World Health Organization fracture prediction guidelines in the United States[40]. However, there is less agreement about when to treat patients who have a bone mineral density in the osteopenic range (a T-score between −1.0 and −2.5), who account for more than half of the patients with fragility fractures[24-26]. The ten-year fracture probabilities calculated with FRAX help to identify a subset of osteopenic patients with a higher fracture risk who will most likely benefit from osteoporosis treatment. For example, a fifty-five-year-old osteopenic woman with a T-score of −2.0 at the femoral neck, a weight of 63.5 kg, a height of 165.1 cm, and no clinical risk factors has a calculated 1.4% ten-year probability of sustaining a hip fracture and an 8.9% ten-year probability of sustaining a major osteoporotic fracture (all ten-year fracture probabilities were derived from the online FRAX tool in August 2009), a level of risk at which treatment should not be considered. Conversely, the calculated ten-year fracture probabilities for a similar patient with a history of a fragility fracture who is being treated with corticosteroid therapy is 5.2% for hip fracture and 25% for a major osteoporotic fracture, a level at which treatment should be started. Therefore, the incorporation of clinical risk factors into FRAX helps inform clinical decision-making.

It must be emphasized that the calculated ten-year fracture probability is only a guideline for treatment decisions. Specific treatment decisions should be individualized. Some clinical risk factors, such as the use of glucocorticoids, have been considered indications for treatment by themselves. The American College of Rheumatology has recommended that patients receive prophylactic bisphosphonate therapy when they undergo treatment with ≥5 mg/day of prednisolone for three months or more and their T-score is less than −1.0[42]. Thus, in this circumstance, treatment should be considered even if the ten-year fracture probability calculated with FRAX is <3% for a hip fracture or <20% for a major osteoporosis-related fracture.

Limitations of FRAX

There are several important limitations that need to be considered when FRAX is used as a calculation tool. The relationships between risk factors and fracture risk incorporated within the FRAX model have been constructed from the primary data of nine population-based cohorts around the world[33,34,38]. Databases from most of the countries incorporated into FRAX provided accurate rates of hip fractures because all patients with a hip fracture are admitted to a hospital. How-

TABLE I Clinical Risk Factors Considered in FRAX

Clinical Risk Factors	Description
Country of residence	As of June 2009, available for Austria, China, France, Germany, Italy, Japan, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States, Argentina, Belgium, Finland, Hong Kong, Lebanon, and New Zealand
Age	Accepts ages between 40 and 90 yr
Sex	
Race	Offered only in the United States: Caucasian, African-American, Hispanic, and Asian
Weight, height, body mass index	Weight in kg and height in cm for calculating body mass index (kg/m^2)
History of fragility fracture	Including radiographic evidence of vertebral compression fracture
Family history of osteoporosis	Hip fracture in mother or father
Current smoking	
Corticosteroid use	Exposed to ≥5 mg/day of prednisolone for ≥3 mo (or equivalent doses of other glucocorticoids)
Rheumatoid arthritis	Diagnosis confirmed by a health-care professional
Secondary osteoporosis	Type-I diabetes, osteogenesis imperfecta in adults, untreated long-standing hypothyroidism and hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease
Alcohol use	>3 units/day (a unit of alcohol is equivalent to a glass of beer [285 mL], an ounce [30 mL] of spirits, or a medium-sized glass of wine [120 mL])

ever, patients with a wrist or proximal humeral fracture are usually treated as outpatients, leading to an underestimation of the incidence of these types of fractures[37]. Assessing the rate of clinical vertebral fracture is also challenging since it is difficult to distinguish between patients with a clinical vertebral fracture and patients who have back pain with an incidental vertebral compression fracture. Therefore, the reported rates of major osteoporotic fractures at sites other than the hip may not be accurate. Kanis et al.[34] studied the use of clinical risk factors to predict osteoporotic fractures on the basis of baseline and follow-up data from nine population-based cohorts. They found that models for predicting hip fractures were substantially better than those for predicting osteoporotic fractures at other sites, regardless of whether the models included bone mineral density alone, clinical risk factors alone, or a combination of both[34,43]. For these reasons, the prediction of the risks of three other major osteoporotic fractures (proximal humeral, wrist, and clinical vertebral fractures) may not be as accurate as the prediction of the risk of hip fracture.

There is also a question of the generalizability of data obtained from the population-based cohorts. For example, the U.S. FRAX model was formulated from data from the Rochester cohort, which was recruited from two random population samples in Olmsted County, Minnesota. This community is predominantly white and is better educated than the white population of the United States as a whole[44]. In addition, recent data have shown that the incidence of hip fracture among Olmsted County residents is declining[45]. Therefore, the incidence and mortality data in the U.S. FRAX model may not reflect current incidence and mortality rates.

The use of FRAX sometimes results in ten-year fracture probabilities that lead to treatment recommendations that contradict those of the National Osteoporosis Foundation. For example, a fifty-year-old postmenopausal woman with a body mass index of 24.1 kg/m^2, no clinical risk factors, and a T-score of −2.5 meets the threshold for pharmacologic therapy on the basis of the T-score; however, the fracture probabilities calculated with the FRAX tool (8.7% for a major osteoporotic fracture and 2.5% for a hip fracture) are below the treatment threshold. Conversely, an eighty-year-old postmenopausal woman with the same body mass index, a parental history of hip fracture, and a T-score of −1.0 has ten-year risks of 26% and 9.9%, respectively, for a major osteoporotic fracture and for a hip fracture—a level of risk at which treatment should be considered. Yet, there is no strong evidence to support treatment of patients with this level of bone mineral density. In

TABLE II 2008 National Osteoporosis Foundation Guidelines for Pharmacologic Treatment of Osteoporosis[39]

Category	Pharmacologic Treatment Should Be Considered
Applicable population	Postmenopausal women and men ≥50 yr of age presenting with:
Previous fracture	Hip or vertebral fracture *or*
Osteopenia	T-score between −1.0 and −2.5 at the femoral neck or spine and a 10-yr probability of a hip fracture of ≥3% or a 10-yr probability of a major osteoporosis-related fracture of ≥20% based on the U.S.-adapted World Health Organization algorithm *or*
Osteoporosis	T-score of −2.5 or less at the femoral neck or spine

addition, FRAX may not accurately predict fracture risk across all age groups[43]. Furthermore, fracture risk probabilities calculated with FRAX are not valid for patients who have already received pharmacologic treatment for osteoporosis such as bisphosphonates.

Other important risk factors for fractures are not included in this calculation tool. These include the serum level of 25-hydroxyvitamin D, physical activity, risk of falls, and biochemical bone markers. Therefore, the calculated risk may be less than the actual risk. In addition, FRAX does not take into account bone mineral density at the spine or the substantially higher risk of spine fracture among those with a history of vertebral compression fractures. A cohort study of 6459 women fifty-five years of age or older with low bone mineral density, of whom 31% (2027) had a radiographically detected vertebral fracture at baseline, demonstrated that a combination of a vertebral fracture on a baseline radiograph, femoral neck bone mineral density, and age predicted incident radiographically evident vertebral fractures significantly better than did use of FRAX and bone mineral density at the femoral neck ($p = 0.0017$)[46]. Nevertheless, FRAX remains an important tool that represents an advance in the care of osteoporosis. The current FRAX model provides an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with bone mineral density. It is anticipated that the limitations described above will be addressed in future FRAX versions.

Assessment of Bone Turnover

Bone turnover is the principal factor that controls both the quality and the quantity of bone in the adult skeleton. An imbalance between bone resorption and bone formation ultimately results in a net loss or gain of the bone tissue. High bone turnover leads to bone loss and an abnormal bone microarchitecture. Conversely, low bone turnover may result in increased bone mass, accumulation of microdamage, and bone fragility. A clinical example of derangement in bone turnover is osteoporosis. Osteoporosis can be categorized into two forms on the basis of bone turnover: low-turnover and high-turnover osteoporosis. The low-turnover state is characterized by a reduction of both bone formative and bone resorptive activities. Conversely, the high-turnover state is characterized by increased activity of osteoclasts, while the activity of osteoblasts may be normal or even increased[47]. The bone-remodeling process is therefore shifted toward bone resorption, resulting in an imbalance of bone turnover that causes osteoporosis. High-turnover osteoporosis is the most common form and occurs in postmenopausal women (so-called primary type-I osteoporosis) or in patients with hyperparathyroidism regardless of their menopausal state[48]. Transient osteoporosis, most commonly seen in men, is also a high-turnover state[49]. Low-turnover osteoporosis occurs in the elderly (so-called age-related osteoporosis, or primary type-II osteoporosis) or following drug interventions, including chemotherapy, corticosteroids, and prolonged bisphosphonate treatment[47,50,51].

Bone turnover can be assessed by measuring biochemical bone markers, categorized as bone formation and bone resorption markers (Table III), in blood and urine samples. Assessment of bone turnover should be considered for patients with osteoporosis, with treatment proceeding accordingly to address each patient's metabolic profile. Bone markers are indicative of bone formation and resorption at one time point and can help in the assessment of medication efficacy as described below.

Bone Resorption Markers

When osteoclasts resorb bone, they degrade the extracellular matrix and release a variety of collagen breakdown products into the circulation that are further metabolized by the liver and kidneys. The collagen degradation products achieve measurable concentrations in both serum and urine (Fig. 3) and are used as indicators of bone resorption. These include the cross-linked aminoterminal-telopeptide (NTX) and cross-linked carboxyterminal-telopeptide (CTX) as well as free pyridinolines (PYD) and deoxypyridinolines (DPD).

Osteoclasts produce the acid phosphatase isoenzyme tartrate-resistant acid phosphatase (TRAP). Total TRAP, however, is influenced by enzymes originating from both erythrocytes and platelets, and its measurement can be impeded by various circulating inhibitors[52]. Currently, a kinetic assay to measure specifically type-5b TRAP, a desialylated isoenzyme present only in osteoclasts and alveolar macrophages, has been described[53,54]. Increased type-5b TRAP levels have been described in conditions associated with increased bone resorption such as end-stage renal failure, hemodialysis bone disease, and metastatic bone disease[55-58].

Bone Formation Markers

During bone formation, osteoblasts produce type-I collagen, which is their major synthetic product. Carboxyterminal propeptide and aminoterminal propeptide of type-I collagen—known as PICP and PINP, respectively—are cleaved from the newly formed collagen molecule and can be measured in serum as indices for type-I collagen biosynthesis. Osteoblasts also secrete a variety of noncollagenous proteins, two of which can be measured clinically as markers of osteoblast activity: bone-specific alkaline phosphatase and osteocalcin. Osteocal-

TABLE III Biochemical Markers of Bone Turnover

Bone Formation Markers	Bone Resorption Markers
Noncollagenous protein: bone-specific alkaline phosphatase and osteocalcin	Produced by osteoclast: tartrate-resistant acid phosphatase (TRAP)
Collagenous protein: carboxyterminal propeptide of type-I collagen (PICP) and aminoterminal propeptide of type-I collagen (PINP)	Collagen degradation products: free and total pyridinolines (PYD), free and total deoxypyridinolines (DPD), serum and urine N-telopeptide of collagen cross-links (NTX), and serum and urine C-telopeptide of collagen cross-links (CTX)

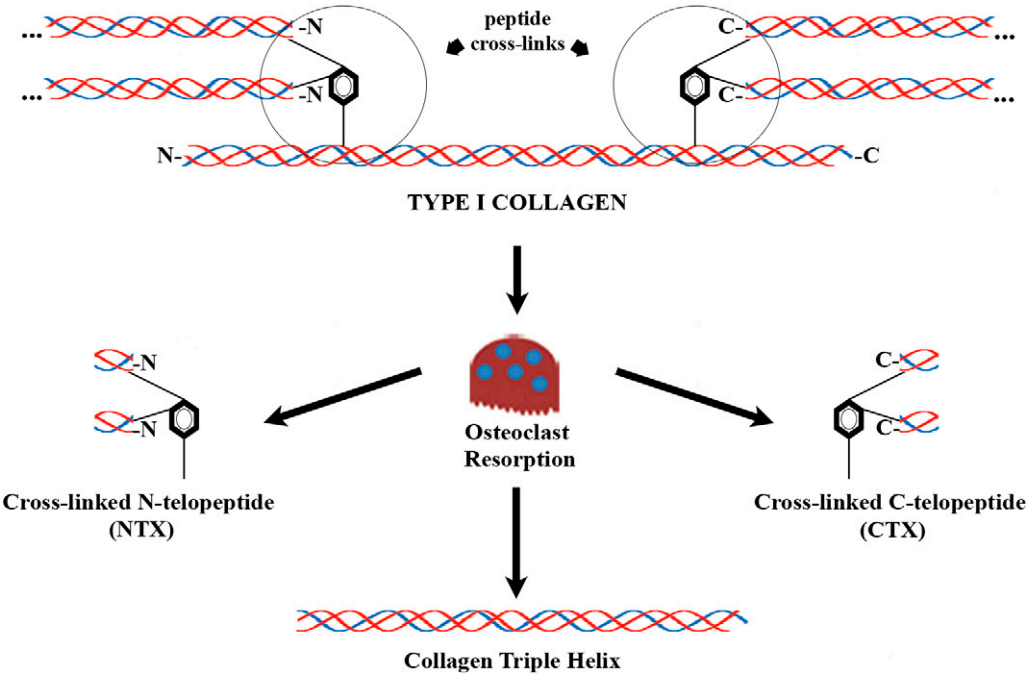

Fig. 3

Both NTX and CTX are reliable markers of bone resorption. During osteoclast-mediated resorption of bone, the collagen molecule is degraded, producing an aminoterminal (or N)-telopeptide, a carboxyterminal (or C)-telopeptide, and a central region of intact triple helix. Cross-linked N-telopeptides and C-telopeptides, known as NTX and CTX, respectively, are specific for bone and achieve a measurable concentration in blood and urine.

cin is a small protein synthesized exclusively by osteoblasts. It is deposited in the bone matrix and can be released into the circulation. Some in vitro studies, however, have suggested that osteocalcin fragments could also be released from osteoclastic degradation of bone matrix and thus may reflect bone resorption[59-61]. In addition, serum osteocalcin levels vary substantially with circadian and other biological factors[62,63]. Therefore, serum osteocalcin is not measured as routinely as are other bone-formation markers.

Alkaline phosphatase is an enzyme found in many tissues including liver and bone, with bone contributing 40% to 50% of the enzyme in normal adults[64]. Although the bone enzyme can be separated from the other forms by laboratory methods, there is a substantial cross-reactivity (±15%) with the liver form, which can be clinically relevant when the patient has liver disease[65]. The half-life of bone-specific alkaline phosphatase is one to two days, making it less sensitive to circadian variation than other markers with a shorter half-life.

Factors Affecting Levels of Bone Formation and Bone Resorption Markers

There are multiple factors that may cause variations in the levels of biochemical bone markers. Therefore, it is necessary to review certain factors that affect bone marker levels before discussing the specific clinical settings in which their measurement might be useful (Table IV). Bed rest, exercise, or fracture-healing can affect the level of bone markers. A prospective study of bone marker levels in 113 elderly women before and after trauma found that the levels were elevated during fracture repair and remained elevated for up to one year[66,67]. Many bone marker levels show substantial variations over a twenty-four-hour period[63,68-70]. All of the urinary and serum bone resorption markers have substantial diurnal variations in levels, which peak between 4:00 A.M. and 8:00 A.M.[71]. For the analysis of urine markers, therefore, it is best to obtain either a twenty-four-hour urine collection or a second morning void sample. In addition, various bone formation or resorption markers have different responses to different disease states and therapies, such as Paget disease, osteomalacia, or glucocorticoid use[51,72,73]. Creatinine excretion also contributes to the overall variability in the levels of urinary bone resorption markers. An alteration in muscle mass, therefore, may alter the urine marker levels. Finally, urine marker levels are not reliable indicators in patients with

TABLE IV Factors Affecting Levels of Markers of Bone Formation and Resorption

Biological Factors	Analytical Factors
Circadian rhythm, seasonal variation, bed rest, exercise, fracture-healing, medical conditions (diabetes mellitus, thyroid diseases, etc.), medications (anticonvulsants, glucocorticoids, etc.)	Technical variability, sample conservation

chronic renal insufficiency; thus, it is preferable to analyze serum bone marker levels in such patients.

Bone markers are also subject to intra-assay and inter-assay variability. With improvements in technical methods, particularly with the introduction of automated immunoassays, the analytical coefficient of variation remains approximately 5%[63]. If possible, measurements for each individual should be performed in the same laboratory[74,75]. Sample conservation is another concern. Serum osteocalcin and TRAP are more labile, whereas collagen peptides and bone-specific alkaline phosphatase are more resistant to degradation[59]. Pyridinoline cross-links are light-sensitive and degrade under the influence of intense ultraviolet irradiation[66].

Potential Clinical Uses of Measurements of Bone Formation and Resorption Marker Levels

Monitoring Effectiveness of Treatment

Currently the best-established clinical use of bone marker analysis is for monitoring treatment efficacy. After antiresorptive therapy, there is a substantial reduction in levels of bone resorption markers within four to six weeks and in levels of bone formation markers within two to three months[76,77]. Antiresorptive agents should produce a reduction in bone resorption markers of between 20% and 80%, depending on the antiresorptive agent used and the markers measured[78-82]. After treatment, the nadir in bone marker levels generally occurs after two to three months and remains constant as long as the patient continues to receive therapy[83]. Therefore, failure to show the expected reduction in levels of bone resorption markers could indicate poor compliance with treatment or an improper use of antiresorptive agents. The objective of treatment should be the return of bone marker levels to the premenopausal range. However, some patients with osteoporosis present with normal bone marker values because the diagnosis was made at a late stage of their disease. In this instance, the goal should be a decrease in bone marker levels to the least significant change. The least significant change, defined as a difference reflecting a real change with a 5% chance of type-1 error (false positive), is approximately 25% to 30% for serum markers and 50% to 60% for urine markers[66].

After treatment with an anabolic agent, levels of bone formation markers increase substantially within four weeks and levels of bone resorption markers increase later, approximately three months following the initial therapy[84,85].

Prediction of Fracture Risk

Prediction of fracture risk is probably the most important potential use of bone marker measurements because turnover alters bone geometry and material properties and thus may affect the susceptibility to fracture. Several studies have shown that bone turnover may be an independent predictor of fracture risk[86-90]. In a study of 671 postmenopausal women, 116 of whom had fractures, high levels of the bone turnover marker bone-specific alkaline phosphatase were independently associated with an increased fracture risk, with an age-adjusted hazard ratio of 2.2 (range, 1.4 to 3.8). The ten-year probability of fracture in osteopenic women was 26% if at least one risk factor (age, an elevated level of bone-specific alkaline phosphatase, or prior fracture) was present compared with 6% in women without any of the three risk factors[26]. In the Os des Femmes de Lyon (OFELY) study, a comparison between baseline bone marker levels in fifty-five women who had a fracture and bone marker levels in 380 women who did not have a fracture within five years before the time of follow-up showed that women with levels of bone resorption markers in the highest quartile had an approximately twofold increased risk of fracture compared with women with levels in the three lowest quartiles. After adjustment for bone mineral density, bone marker levels were still predictive of fracture risk, with similar relative risks of 1.7 to 2.3. This finding indicates that bone turnover markers and bone mineral density predict fracture risk independently. When both factors are altered, the fracture risk is compounded[91]. Although bone markers are independent predictors of fracture risk, the optimal use of bone marker measurements alone or in combination with bone mineral density in predicting absolute fracture risk has not yet been established.

Selection of Patients for Treatment

Several studies indicate that individuals with the highest levels of bone turnover seem to have the best response to antiresorptive therapy[83,92]. The relationship between bone marker levels and the response to antiresorptive agents, however, is controversial[93-96]. The authors of a pharmacoeconomic study concluded that measurement of bone marker levels has the potential to identify a subset of postmenopausal women with bone marker levels within the highest quartile, but who do not have osteoporosis as defined by the World Health Organization, for whom alendronate treatment to prevent fracture is cost-effective[95]. In a study assessing the efficacy of risedronate in the treatment of postmenopausal osteoporosis in 1593 women, the reduction in the incidence of vertebral fractures was independent of the baseline measurement of the urinary deoxypyridinoline level. However, the number needed to treat to avoid one vertebral fracture at twelve months was fifteen with high urinary deoxypyridinoline levels and twenty-five with low urinary deoxypyridinoline levels[93]. Therefore, from a pharmacoeconomic standpoint, it may be useful to stratify patients by the pretreatment bone resorption rate[93,94].

With regard to anabolic therapy, a recent post hoc analysis of the data from the Fracture Prevention Trial study, in which teriparatide was used to treat osteoporosis, showed a strong positive correlation between the baseline bone markers PINP, NTX, PICP, bone-specific alkaline phosphatase, and deoxypyridinoline and subsequent increases in lumbar spine bone mineral density at eighteen months[97]. Therefore, even patients with high bone turnover rates at baseline could have a robust bone mineral density response to teriparatide treatment[97].

Overview

Osteoporotic fracture is a common and debilitating problem in the elderly. However, if physicians can identify patients at risk

for fracture, prevention programs may be initiated to reduce the number of fractures sustained. Although bone mineral density is used for the diagnosis of osteoporosis and to assess fracture risk, it has become increasingly apparent that bone mineral density reflects only one component of bone strength. Recently, FRAX was developed to calculate age-specific fracture probabilities in men and women on the basis of clinical risk factors and the bone mineral density at the femoral neck. Treatment of osteoporosis should be considered for patients with low bone mineral density and a ten-year risk of hip fracture of ≥3% or a ≥20% ten-year risk of a major osteoporosis-related fracture, as assessed with FRAX. Measurements of biochemical bone marker levels can be used not only to monitor treatment efficacy but also to assess fracture risk and help select patients for therapy. Antiresorptive medications are most appropriate for patients with high bone turnover, while anabolic agents demonstrate efficacy in both low and high-turnover conditions. It is anticipated that the development of new imaging tools to evaluate bone quality will improve the assessment of a patient's fracture risk and response to treatment in the future. In the meantime, bone strength should be assessed with the use of clinical risk factors (as identified in FRAX) and measurement of bone turnover marker levels as a supplement to the measurement of bone mineral density to enhance patient evaluation and improve osteoporosis diagnosis and treatment. ■

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