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# Approach to the Screening and Diagnosis of Osteoporosis

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## 1. Introduction

The goal of treatment of osteoporosis is to decrease the risk of fractures in patients with high risk for a first or subsequent fracture. The efficacy of treatment will depend on the efficacy and level of accomplishment of case finding to select patients at risk, the results of additional investigations, the efficacy, tolerance, and safety of medical intervention, and the adherence to treatment during follow-up. Each of these steps is critical in treatment in daily clinical practice. Failure to consider one or other step can result in suboptimal fracture prevention or overtreatment (Geusens, 2009).

On the other hand, measurement of bone mineral density (BMD), assessment of the fracture risk, and making decisions regarding to appropriate therapeutic intervention are the ultimate goal when evaluating patients for osteoporosis (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). Since many fractures among postmenopausal women occur in those with T-scores better than in the osteoporotic range (Siris et al, 2004; Schuit et al, 2004; Cranney et al, 2007), screening of the patients at high risk of fracture and early diagnosis are important.

## 2. Screening of osteoporosis

The aim of screening is obviously to direct interventions to those most in need, and to avoid treatment of healthy individuals who will never fracture. Bone mass is used conventionally as a proxy of overall bone strength and low bone mass is a major risk factor for osteoporotic fractures. Although BMD measurement is the standard test for the diagnosis of osteoporosis before fracture, ongoing research indicates that BMD measurement alone may not be adequate for detection of individuals at high risk of fracture (Kanis, 1994). Epidemiological studies have shown that a substantial proportion of osteoporotic fractures occur in postmenopausal women who do not meet BMD criteria for osteoporosis defined according to the WHO definition as a T-score of -2.5 or below (Siris et al, 2004; Schuit et al, 2004; Cranney et al, 2007). This suggests that factors other than BMD contribute to a patient's risk of fracture. Central dual-energy x-ray absorptiometry (DXA) is not available everywhere. Furthermore, although BMD measurement is specific, it lacks sensitivity when used alone, so that a number of high-risk patients escape identification (Kanis, 1994). Thus, the potential

impact of extensive population-based screening with BMD in women at the time of menopause on the burden of fractures is less than optimal; screening the general population with BMD would not be cost-effective and is considered inadvisable in many countries (World Health Organization [WHO], 2004). In practice, most guidelines recommend using risk factor assessment tools such as Fracture Risk Assessment Tool FRAX® to help select patients for BMD measurement and/or treatment.

The National Osteoporosis Foundation (NOF), US Preventive Services Task Force (USPSTF), and the American Association of Clinical Endocrinologists (AACE) recommend that BMD testing should be performed to guide treatment decisions, based on the patient's risk profile (National Osteoporosis Foundation [NOF], 2003; US Preventive Services Task Force [USPSTF], 2002; Hodgson et al, 2001). Also, the NOF recommends that all postmenopausal women and men age 50 and older should be evaluated clinically for osteoporosis risk in order to determine the need for BMD measurement and considered the possibility of osteoporosis and fracture risk in men and women, based on the presence of the risk factors and conditions (NOF, 2010).

The National Osteoporosis Guideline Group (NOGG) recommends that patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant clinical risk factors because, at present, there is no universally accepted policy for population screening in the UK to identify individuals with osteoporosis or those at high risk of fracture (Compston et al, 2009).

## 3. Diagnosis of osteoporosis

Osteoporosis is diagnosed on the basis of either a low-impact or fragility fracture or a low BMD. A low-impact fracture is one that occurs after a fall from standing height or less; a fragility fracture occurs spontaneously or with no trauma (cough, sneezing, sudden movement) (Mauck & Clarke, 2006).

Until recent years, diagnosis of non-fractured patients was based on the quantitative assessment of BMD, usually by central DXA. In 1994, the World Health Organization (WHO) developed a definition of osteoporosis on the basis of studies of women of various ages (Table 1) (Kanis et al, 1994). The BMD, measured with DXA, results are reported as a density measurement in $gm/cm^2$, in addition to T- and Z-scores.

| Category | Fracture Risk | Action |
|---|---|---|
| Normal<br>T-score at -1.0 or above | Below average | Be watchful for clinical triggers |
| Osteopenia<br>T-score between<br>-1.0 and -2.5 | Above average | Consider prevention in peri- or post-MPW<br>Be watchful for clinical triggers<br>Possibly repeat investigations in 2-3 years |
| Osteoporosis<br>T-score at -2.5 or below | High | Exclude secondary causes<br>Therapeutic intervention indicated in most patients |
| Severe Osteoporosis<br>T-score at -2.5 or below and<br>already experienced one or<br>more fractures | Established osteoporosis | Exclude secondary causes<br>Therapeutic intervention indicated in most patients |

Table 1. Definition of osteoporosis by the WHO

The T-score represent the number of SDs from the mean bone density values in normal gender-matched young adults. T-score is used to make a diagnosis of normal bone density, osteoporosis or osteopenia in postmenopausal women and in men age 50 years and older (Leib et al, 2004). Z-scores represent the number of SDs from the normal mean value for age- and gender-matched control subjects. A Z-score of -2.0 or lower may suggest the presence of a secondary cause of osteoporosis, although no definitive data support this hypothesis. Z-scores are used preferentially to assess bone loss in premenopausal women and men younger than age 50 years. A Z-score of -2.0 or lower is defined as "below the expected range for age"; a Z-score above -2.0 is "within the expected range for age." (Leib et al, 2004). Originally, the definition of osteoporosis was developed for the estimation of the prevalence of osteoporosis across populations. It was not for the assessment of osteoporosis in individual patient. In other words, diagnostic thresholds differ from intervention thresholds. The fracture risk varies at different ages, even with the same T-score. Other factors that determine intervention thresholds include the presence of clinical risk factors (CRFs), costs and and benefits of treatment.

## 4. Determination of fracture risk

In the past decade, a great deal of research has taken place to identify factors other than BMD that contribute to fracture risk. The consideration of well-validated CRFs, with or without BMD, is likely to improve fracture risk prediction and the selection of individuals at high risk for treatment. Some of these risk factors act independently of BMD to increase fracture risk whereas others increase fracture risk through their association with reduced BMD (e.g., some of the secondary causes of osteoporosis) (Table 2) (Compston et al, 2009).

Several models have been proposed to stratify osteoporotic fracture risk. These include strategies to identify patients with a high risk of low BMD (e.g., the OST index (Gensens et al, 2002), and the FRAX algorithm (Kanis, et al, 2008a, 2008b)) or with a high absolute risk of fractures based on CRFs, with or without BMD (e.g., FRAX algorithm (Kanis, et al, 2008a, 2008b)), Fracture Risk in Glucocorticoid Users (FIGS) (van Staa et al, 2005), the Garvan algorithm (Nguyen et al, 2008)), and simplified questionnaires.

Among these models, FRAX®, developed by WHO is an algorithm for individualized fracture risk prediction which is depend on population-based cohort from Europe, North America, Asia, and Australia.

### 4.1 Use of WHO Fracture Risk Assessment Tool (FRAX®)

FRAX® is a clinical tool for case finding for identifying patients at high risk for fractures, for selecting patients to measure BMD, and for treatment decisions. FRAX® should not be considered a gold standard but rather provides an aid to enhance patient assessment. The aim of FRAX® is to provide an assessment tool for the fracture prediction with use of CRFs with or without femoral neck BMD (Kanis et al, 2008a). These CRFs include age, sex, race, height, weight, body mass index (BMI), a history of fragility fracture, a parental history of hip fracture, use of oral glucocorticoid, rheumatoid arthritis, and other secondary causes of osteoporosis, current smoking, and alcohol intake of three or more units daily. These risk factors were identified and validated based on an analysis of 12 prospective studies, yielding a total of 250,000 person-years in 60,000 men and women with more than 5,000 osteoporotic fractures (Kanis, 1994). Because fracture probability also varies markedly among different regions of the

world, FRAX® allows fracture risk to be calculated for countries where the incidences of both fractures and mortality are known (Unnanuntana et al, 2010).

FRAX® has been developed for calculating the 10-year absolute fracture risk in individual patients in primary care settings for a major osteoporotic fracture (in the proximal humerus, the wrist, or the hip or a clinical vertebral fracture) and for a hip fracture calibrated to the fracture and death hazards. The relative risks are difficult to apply in clinical practice since their clinical significance depends on the prevalence of fractures in the general population. As a result, the concept of the absolute risk of fractures has emerged and refers to the individual's risk for fracture over a certain time period, e.g., over the next 5 or 10 years which is the usual duration of the effects of osteoporosis medications during and after use (van Geel et al, 2010).

The FRAX® algorithm is available at www.nof.org and at www.shef.ac.uk/FRAX. FRAX® is intended for postmenopausal women and men age 50 and older who have not been treated for osteoporosis; it is not intended for use in younger adults or children.

NOF starts case finding with age as a criterion (NOF, 2011). Below 65 years, NOF advocates clinical attention for the presence of CRFs (those included in FRAX, with the addition of other risks), and a DXA in the presence of CRFs. In all women older than 65 years, NOF advocates BMD. Treatment is advocated in women with osteoporosis or osteoporotic fracture and in women with osteopenia if FRAX® calculation with BMD indicates a high risk of fracture or when specific high risks (total immobilization and glucocorticoid use) are present.

| |
| --- |
| Age |
| Sex |
| Low body mass index ($\leq$19 kg/m$^2$) |
| Previous fragility fracture, particularly of the hip, wrist, and vertebrae including morphometric vertebral fracture |
| Parental history of hip fracture |
| Current glucocorticoid treatment (any dose, per oral for $\geq$3 months) |
| Current smoking |
| Alcohol intake of 3 or more units daily |
| Secondary causes of osteoporosis including: |
|     Rheumatoid arthritis |
|     Untreated hypogonadism in men and women |
|     Prolonged immobility |
|     Organ transplantation |
|     Type 1 diabetes |
|     Hyperthyroidism |
|     Gastrointestinal disease |
|     Chronic liver disease |
|     Chronic obstructive pulmonary disease |
| Falls* |

* Not presently accommodated in the FRAX® algorithm

Table 2. Clinical risk factors used for the assessment of fracture probability

The National Osteoporosis Society (NOS) starts case finding with CRFs of FRAX® in all postmenopausal women (Compston et al, 2009). Treatment is advocated in high-risk patients based on CRFs of FRAX® without DXA and in patients with intermediate risk when BMD results integrated in FRAX® indicate a high risk.

It should also be acknowledged that there are many other risk factors for fracture that are not incorporated into assessment algorithms. FRAX® does not include fall-related risk factors and other risk factors for fractures: dose and duration of some risk factors like glucocorticoid use; characteristics of previous fractures (location, number, and severity); vitamin D deficiency; and levels of biochemical markers of bone turnover (van Geel et al, 2010). Moreover, no randomized clinical trials focusing on prevention of fractures in patients who are included based on FRAX® are available (van Geel et al, 2010). Further studies will be needed on the ability to treatment to reduce fracture risk in subjects at high risk for fractures based on FRAX®. Another drawback is that FRAX® is only applicable in treatment naïve patients (Saag, 2009).

## 5. Clinical investigations

Comprehensive approach to the clinical evaluation of osteoporosis is recommended. A detailed history and physical examination together with BMD assessment and the 10-year estimated fracture probability are utilized to establish the individual patient's risk. The range of tests will depend on the severity of the disease, age at presentation, and the presence or absence of fractures. The aims of patient evaluation are to exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma), identify the cause of osteoporosis and contributory factors, assess the risk of subsequent fractures and select the most appropriate form of treatment (Compston et al, 2009).

### 5.1 History and physical examination

Many metabolic bone diseases are associated with low BMD, therefore a complete and thorough history taking and physical examination are essential to establishing a correct diagnosis of osteoporosis. A complete history should be obtained, with specific attention given to the risk factors, including lifestyle, medical, family, and medication histories (Table 3) (NOF, 2010). Physical examination should include height and weight for BMI and determining any loss of height (historical height loss >4 cm). A thorough physical examination may detect kyphosis, a protruding abdomen, rib-iliac crest distance of less than 2 cm, height loss (prospective height loss >2 cm), acute or chronic back pain and/or tenderness, reduced gait speed or grip strength, and poor visual acuity. Certain other findings, such as nodular thyroid, hepatic enlargement, jaundice, or cushingoid features may reveal secondary causes of osteoporosis (Lane, 2006).

Since the majority of osteoporosis-related fractures result from falls, it is also important to evaluate risk factors for falling. The most important of these seem to be a personal history of falling, along with muscle weakness and gait, balance and visual deficits (Anonymous, 2001). All elderly should be asked annually about the occurrence of falls. Any patient who reports a single fall should undergo basic evaluation of gait/balance (e.g., "Get Up and Go test")(Anonymous, 2001). Items that should be included as a part of a fall risk assessment are summarized in Table 4 (NOF, 2010).

| Lifestyle factors | | |
|---|---|---|
| Low calcium intake | Vitamin D insufficiency | Excessive vitamin A |
| High caffeine intake | High salt intake | Aluminum (in antacid) |
| Alcohol (≥3 units/day) | Inadequate physical activity | Immobilization |
| Smoking | Falling | Thinness |
| **Genetic factors** | | |
| Cystic fibrosis | Homocysteinuria | Osteogenesis imperfecta |
| Ehlers-Danlos | Hypophosphatasia | Parental history of hip fracture |
| Gaucher's disease | Idiopathic hypercalciuria | Porphyria |
| Glycogen storage disease | Marfan syndrome | Riley-Day syndrome |
| Hemochromatosis | Menkes steely hair syndrome | |
| **Hypogonadal states** | | |
| Androgen insensitivity | Hyperprolactinemia | Turner's & Klinefelter's syndromes |
| Anorexia nervosa, 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, lymphoma | 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 loss |
| Congestive heart failure | Idiopathic scoliosis | Prior fracture as an adult |
| Depression | Multiple sclerosis | Sarcoidosis |
| **Medications** | | |
| Anticoagulants (heparin) | Chemotherapeutic drugs | GnRH agonists |
| Anticonvulsants | Cyclosporin A, tacolimus | Lithium |
| Aromatase inhibitors | Depo-medroxyprogesterone | Barbiturates |
| Glucocorticoid | Selective serotonin reuptake inhibitors | Thiazolidinediones |
| Proton pump inhibitors | | |

Table 3. Conditions, diseases, and medications that cause or contribute to osteoporosis and fractures

| Environmental risk factors |
| --- |
| Lack of assistive devices in bathrooms<br>Loose throw rugs<br>Low level lighting<br>Obstacles in the walking path<br>Slippery outdoor conditions |
| Medical risk factors |
| Age<br>Anxiety and agitation<br>Arrhythmia<br>Dehydration<br>Depression<br>Female gender<br>Impaired transfer and mobility<br>Malnutrition<br>Medications causing oversedation (narcotic analgesics, anticonvulsants, psychotropics)<br>Orthostatic hypotension<br>Poor vision and use of bifocals<br>Previous fall<br>Reduced problem solving or mental acuity and diminished cognitive skills<br>Urgent urinary incontinence<br>Vitamin D insufficiency (25(OH)D <30 ng/mL (75 nmol/L) |
| Neuro and musculoskeletal risk factors |
| Kyphosis<br>Poor balance<br>Reduced proprioception<br>Weak muscles |
| Other risk factors |
| Fear of falling |

Table 4. Risk factors for falls

## 5.2 Bone mineral density measurement

Although central DXA of the hip (femoral neck or total hip) is the gold standard for diagnosing osteoporosis, many experts including the International Society for Clinical Densitometry (ISCD), recommend using the lowest central DXA T-score of posteroanterior lumbar spine (L1-L4), femoral neck, or total hip (or the 33% distal radius of the non-dominant forearm, if measured) to make the diagnosis (Leib et al, 2004). DXA measurement of BMD at other sites (including the trochanter, Ward triangle, lateral lumbar spine, other forearm regions, heel, or total body) or with other technologies (calcaneal ultrasonography, peripheral DXA, quantitative computed tomography, single- or dual-photon radionuclide absorptiometry, or magnetic resonance imaging) are not recommended for use in diagnosing osteoporosis (Leib et al, 2004; Marshall et al, 1996).

As a spine region of interest, posteroanterior L1-L4 for spine BMD measurement and only exclude vertebrae that are affected by local structural change (e.g., degenerative change or compression fracture) or artifact should be used (Baim et al, 2008). However, BMD based diagnostic classification should not be made using a single vertebra. If only one evaluable vertebra remains after excluding other vertebrae, diagnosis should be based on different valid skeletal site.

As a hip region of interest, femoral neck or total proximal femur, whichever is lowest should be used (Baim et al, 2008). Forearm BMD should be measured under the following circumstances: hip and/or spine cannot be measured or interpreted; hyperparathyroidism; and very obese patients (over the weight limit for DXA table) (Baim et al, 2008).

Peripheral DXA (pDXA), quantitative computed tomography (QCT), and quantitative ultrasound densitometry (QUS) are also capable of predicting both site-specific and overall fracture risk (NOF, 2010). When performed according to accepted standards, these densitometry techniques are accurate and highly reproducible (USPSTF, 2002). However, T-scores from these technologies cannot be used according to the WHO diagnostic classification because they are not equivalent to T-scores derived from DXA (NOF, 2010). Moreover, these measurements are less useful in predicting the risk of fractures of the spine and proximal femur than central DXA (Lane, 2006).

The accuracy of QCT of the spine in predicting spinal fracture is comparable to that of DXA but has the advantage of measuring true volumetric or 3-dementional BMD, in contrast to the areal BMD obtained from DXA (Miller, 1999). QCT can distinguish between cortical and trabecular bone and thus is more sensitive to changes in BMD caused by the higher bone turnover rate of trabecular bone (Brunader & Shelton, 2002). It is also precise enough to detect BMD changes over time, and it can be used to follow the disease state or to monitor the response of osteoporosis therapy (Brunader & Shelton, 2002). For this reason, QCT are not the gold standard at the moment, but are also recommended (if applicable) to evaluate osteoporosis.

## 5.3 Vertebral fracture assessment

Morphometric vertebral fractures are the most frequent fractures in women and men older than 50 years (Sambrook & Cooper, 2006). Independent of BMD, age, and other CRFs, radiographically confirmed vertebral fracture is a strong predictor of future vertebral, non-vertebral, and hip fracture risk (Lems, 2007). The presence of a vertebral fracture increases the relative risk of future vertebral fractures by 4.4-fold and increases the risk of fragility fractures at other skeletal sites as well (Klotzbuecher et al, 2000). The higher the grade (severity) of the existing vertebral fracture, or the more vertebral fractures present (one, two, or three), the greater the risk for future fractures (Gallagher et al, 2005; Black et al, 1999).

Clinical vertebral fractures represent one out of three to four morphometric vertebral fractures (van Helden et al, 2008). Because most morphometric vertebral fractures are not diagnosed until clinically suspected and imaging by x-ray is performed, vertebral fractures are often missed.

Imaging techniques to detect and evaluate vertebral fractures in clinical practice include plain radiography (x-ray), computed tomography (CT), magnetic resonance imaging (MRI) nuclear bone scanning, and vertebral fracture assessment (VFA). There are differences in each of these in terms of imaging resolution, radiation exposure, availability, cost, and patient convenience.

Vertebral Fracture Assessment (VFA) is a new method to evaluate the presence of morphometric vertebral fractures and deformities using central DXA. VFA reliably and accurately identified patients with vertebral fractures that have not been recognized, with greater patient convenience, lower cost, and less radiation than standard x-ray. VFA is indicated when there is a probability that a prevalent vertebral fracture will influence clinical management of the patient (Lewiecki & Laster, 2006). The use of VFA contributes to better define the fracture risk in women with osteopenia and contributes to treatment decisions identifies patients at high risk of fractures in the absence of BMD-based osteoporosis. Indications for VFA according to the ISCD are presented in Table 5 (Baim et al, 2008).

| Postmenopausal women with low bone mass (osteopenia) by BMD criteria, plus any one of the following: |
| --- |
| Age ≥70 years<br>Historical height loss >4 cm (1.6 inch)<br>Prospective height loss >2 cm (0.8 inch)<br>Self-reported vertebral fracture (not previously documented)<br>Two or more of the following:<br>    Age 60-69 years<br>    Self-reported prior non-vertebral fracture<br>    Historical height loss of 2 to 4 cm<br>    Chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe chronic obstructive pulmonary disorder (COPD) or chronic obstructive airway disease (COAD), seropositive rheumatoid arthritis, Crohn's disease) |
| Men with low bone mass (osteopenia) by BMD criteria, plus any one of the following: |
| Age ≥80 years<br>Historical height loss >6 cm (2.4 inch)<br>Prospective height loss >3 cm (1.2 inch)<br>Self-reported vertebral fracture (not previously documented)<br>Two or more of the following:<br>    Age 70-79 years<br>    Self-reported prior non-vertebral fracture<br>    Historical height loss of 3 to 6 cm<br>    On pharmacologic androgen deprivation therapy or following orchiectomy<br>    Chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease) |
| Women or men on chronic glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for 3 months or longer) |
| Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management |

Table 5. Indications for vertebral fracture assessment using x-ray absorptiometry

## 5.4 Biochemical markers of bone turnover

Bone turnover is the principal factor that controls both the quality and the quantity of bone in adult skeleton and it can be assessed by measuring biochemical markers in blood and urine samples. Bone turnover markers (BTMs) represent the products of bone formation and resorption that are released into the circulation (Table 6).

| Resorption markers |
| --- |
| Urine<br>    N-telopeptide cross-links of type 1 collagen (uNT$_X$)<br>    C-telopeptide cross-links of type 1 collagen (uCT$_X$)<br>    Pyridinolines, free and total (Pyr)<br>    Deoxypyridinolines, free and total (Dpd) |
| Serum<br>    N-telopeptide cross-links of type 1 collagen (sNT$_X$)<br>    C-telopeptide cross-links of type 1 collagen (sCT$_X$)<br>    Cross-linked C-telopeptide of type 1 collagen (ICTP)<br>    Tartrate-resistant acid phosphatase (TRAP) |
| Formation markers |
| Serum<br>    Bone specific alkaline phosphatase (BSAP)<br>    Osteocalcin (OC)<br>    Amino-terminal propetide of type 1 collagen (P1NP)<br>    Carboxy-terminal propetide of type 1 collagen (P1CP) |

Table 6. Markers of bone turnover

Quantitative changes in BTMs reflect the dynamic process of bone metabolism. BTMs have been associated with increased osteoporotic fractures independently of BMD in large prospective studies. They also may predict bone loss and, when repeated after 3 to 6 months of treatment with FDA approved antiresorptive drugs, may be predictive of fracture risk reduction. However, BTMs are not a substitute for DXA in women at risk. The value of BTMs in the assessment of fracture risk is likely to be in combination with risk factors, including BMD (Delmas et al, 2000). Generally, their use in the diagnosis of osteoporosis is not recommended (Lash et al, 2009).

There are multiple factors that may cause variations in the levels of BTMs (Table 7). Therefore it is necessary to review certain factors that affect bone marker levels. The main source of variability is pre-analytical; mostly sample conservation and biological variability (Unnanuntana et al, 2010). Pyridinoline crosslinks are light sensitive and degraded under the influence of intense UV irradiation (Body et al, 2009). Osteocalcin concentrations are decreased by freeze-thaw cycles and hemolysis. Assays detecting only intact osteocalcin are particularly affected by in vitro degradation, so it may be advantageous to use assays recognizing both the intact molecule and the large N-terminal fragment (N-MID, 1–43 amino acid), which appear to be more stable, sensitive and reproducible. (Delmas et al, 1985) Some osteocalcin fragments are also released during bone resorption (Delmas et al, 1990). In adults, the main source of undesirable biological variability is the circadian rhythm, with higher values in the early morning hours (peak in 4:00 A.M. and 8:00 A.M.), then a steep decrease in the morning, to attain a nadir at the end of the afternoon (through in 1:00 P.M. and 11:00 P.M.) (Seibel et al, 2005). Most BTMs follow the same pattern, with the exception of alkaline phosphatase because of its longer half-life. Practically, it implies that the measurement of BTMs must be performed in the same lab using standard procedures; samples should be taken while fasting and always at the same time of day. For the urinary BTMs, it is best to obtain either a 24-hour urine collection or morning second voided urine sample. Creatinine excretion also contributes to the overall variability in the levels of urinary BTMs (Unnanuntana et al, 2010).

| Biological factors | Analytical factors |
|---|---|
| Uncontrollable | Technical variability |
|    Age | Sample conservation and processing |
|    Sex | |
|    Growth | |
|    Menopausal status | |
|    Immobilization | |
|    Recent fracture | |
|    Compromised renal and/or hepatic function | |
|    Medical conditions (diabetes, thyroid disease, etc.) | |
|    Medications (anticonvulsants, GnRH agonists, glucocorticoids, etc.) | |
| Controllable | |
|    Circadian rhythm | |
|    Menstrual cycle | |
|    Exercise | |
|    Food intake | |
|    Seasonal variation | |
|    Sample handling | |

Table 7. Factors affecting levels of bone turnover markers

### 5.5 Laboratory tests

Among men, 30% to 60% of osteoporosis cases are associated with secondary cause. Among perimenopausal women, more than 50% of cases are associated with secondary causes (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). In patients referred for DXA in the clinical context of an osteoporosis clinic, contributors to secondary osteoporosis were already documented in one out of three postmenopausal women, previously undiagnosed contributors were found in an additional 30% of women (Tannenbaum et al, 2002).

General consensus exists among experts that a minimum screening laboratory tests should be considered for all patients who are diagnosed as having osteoporosis prior to treatment. Many experts have also suggested that patients who have osteoporosis and a Z-score of less than -2.0 should have more extensive laboratory tests for secondary cause of osteoporosis. A diagnosis of osteoporosis in men should also prompt a through work-up for secondary causes regardless of their Z-score (Mauck & Clarke, 2006).

The range of laboratory tests will depend on the severity of the disease, age at presentation, and the presence or absence of fractures. In patients with BMD-based osteoporosis or presenting with a clinical fracture or both, diagnostic evaluation is necessary and should include blood cell count, sedimentation rate or C-reactive protein, serum calcium, phosphate, alkaline phosphatase, liver transaminase, albumin, creatinine, thyroid stimulating hormone (TSH) and $25(OH)D_3$. According to the clinical features and suspicion, other measurements such as parathyroid hormone (PTH), protein immunolelectrophoresis and urinary Bence-Jones proteins, serum testosterone, sex-hormone binding globulin (SHBG), follicle stimulating hormone (FSH), and luteinizing hormone (LH) in men, serum prolactin, 24-hour urinary cortisol/dexamethasone suppression test, endomysial and/or tissue transglutaminase antibodies, 24-hour urinary calcium and creatinine looking for secondary causes are indicated (Compston et al, 2009). If a specific secondary cause of osteoporosis is suspected on the basis of the history and physical examination findings, further direct testing is indicated.

## 6. Conclusion

Many factors are associated with osteoporosis and fracture, including low peak bone mass, hormonal factors, the use of certain medications, cigarette smoking, low physical activity, low calcium and vitamin D intake, race, small body size, and a personal or family history of fracture. All these factors should be taken into account when assessing the risk of fracture to determine which patients require further assessment and/or treatment. Clinical guidelines help guide practice but should not replace clinical judgment and patient preferences. The final decision about screening, assessment, and/or treatment is ultimately at the discretion of the physician and the patient.
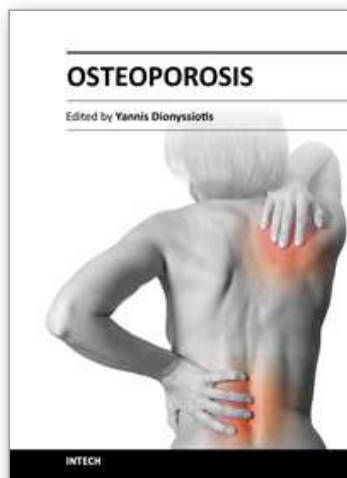
## 7. References

Anonymous. (2001). Guideline for the prevention of falls in older persons. *Journal of American Geriatric Society*, Vol.49, No.5, pp. 664-672, ISSN 0002-8614

Baim, S ; Binkley, N. Bilezikian, J.P. Kendler, D.L. Hans, D.B. Lewiecki, E.M. & Silverman, S. (2008). Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. *Journal of Clinical Densitometry*, Vol.11, No.1, pp. 75-91, ISSN 1094-6950

Black, D.M.; Arden, N.K. Palermo, L. Pearson, J. & Cummings, S.R. (1999). Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *Journal of Bone and Mineral Research*, Vo.14, No.5, pp. 821-828, ISSN 0884-0431

Body, J.J.; Bergmann, P. Boonen, S. Boutsen, Y. Devogelaer, J.P. Goemaere, S. Kaufman, J.M. Rozenberg, S. & Reginster, J.Y. (2010). Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. *Osteoporosis International,* Vol.21, No.10, pp. 1657-1680, ISSN 0937-941X

Brunader, R. & Shelton, D.K. (2002). Radiologic bone assessment in the evaluation of osteoprosis. *American Family Physician*, Vol.65, No.7, pp. 1357-64, ISSN 0002-838X

Compston, J.; Cooper, A. Cooper, C. Francis, R. Kanis, J.A. Marsh, D. McCloskey, E.V. Reid, D.M. Selby, P. Wilkins, M. & National Osteoporosis Guideline Group (NOGG). (2009). Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas*, Vol.62, No.2, pp. 105-108, ISSN 0378-5122

Cranney, A.; Jamal, S.A. Tsang, J.F. Josse, R.G. & Leslie, W.D. (2007). Low bone mineral density and fracture burden in postmenopausal women. *Canadian Medical Association Journal*, Vol.177, No.6, pp. 575-580, ISSN 0820-3946

Delmas, P.D.; Christiansen, C. Mann, K.G. & Price, P.A. (1990). Bone Gla protein (osteocalcin) assay standardization report. *Journal of Bone and Mineral Research*, Vol.5, No.1, pp. 5-11, ISSN 0884-0431

Delmas, P.D.; Eastell, R. Garnero, P. Seibel, M.J. Stepan, J. & Committee of Scientific Advisors of the International Osteoporosis Foundation. (2000). The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. *Osteoporosis International*, Vol.11, Suppl 6, pp. S2-17, ISSN 0937-941X

Delmas, P.D.; Malaval, L. Arlot, M.E. & Meunier, P.J. (1985). Serum bone Gla-protein compared to bone histomorphometry in endocrine diseases. *Bone,* Vol.6, No.5, pp. 339-341, ISSN 8756-3282

Gallagher, J.C.; Genant, H.K. Crans, G.G. Vargas, S.J. & Krege, J.H. (2005). Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. *The Journal of Clinical Endocrinology and Metabolism*, Vo.90, No.3, pp. 1583-1587, ISSN 0021-972X

Geusens, P.; Hochberg, M.C. van der Voort, D.J. Pols, H. van der Klift, M. Siris, E. Melton, M.E. Turpin, J. Byrnes, C. & Ross, P. (2002). Performance of risk indices for identifying low bone density in postmenopausal women. *Mayo Clinic Proceedings,* Vol.77, No.7, pp. 629-637, ISSN 0025-6196

Geusens, P. (2009). Strategies for treatment to prevent fragility fractures in postmenopausal women. *Best Practice & Research. Clinical Rheumatology*, Vol.23, No.6, pp. 727-740, 1521-6942, ISSN 1521-6942

Hodgson, S.F.; Watt,s N.B. Bilezikian, J.P. Clarke, B.L. Gray, T.K. Harris, D.W. Johnston, C.C. Jr. Kleerekoper, M. Lindsay, R. Luckey, M.M. McClung, M.R. Nankin, H.R. Petak, S.M. Recker, R.R. & AACE Osteoporosis Task Force. (2003). American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. *Endocrine Practice,* Vol.9, No.6, pp. 544-564, ISSN 1530-891X

Kanis, J.A.; Burlet, N. Cooper, C. Delmas, P.D. Reginster, J.Y. Borgstrom, F. Rizzoli, R. & European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). (2008). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis International,* Vol.19, No.4, pp. 399-428, ISSN 0937-941X

Kanis, J.A.; McCloskey, E.V. Johansson, H. Strom, O. Borgstrom, F. Oden, A. & National Osteoporosis Guideline Group. (2008). Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. *Osteoporosis International,* Vol.19, No.10, pp. 1395-1408, ISSN 0937-941X

Kanis, J.A.; Melton, L.J. 3rd. Christiansen, C. Johnston, C.C. & Khaltaev, N. (1994). The diagnosis of osteoporosis. *Journal of Bone and Mineral Research,* Vol.9, No.8, pp. 1137-1141, ISSN 0884-0431

Kanis, J.A.; Oden, A. Johansson, H. Borgström, F. Ström, O. & McCloskey, E. (2009). FRAX and its applications to clinical practice. *Bone,* Vol.44, No.5, pp. 734-743, ISSN 8756-3282

Kanis, J.A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporosis International,* Vol.4, No.6, pp. 368-381. ISSN 0937-941X

Klotzbuecher, C.M.; Ross, P.D. Landsman, P.B. Abbott III, T.A. & Berger, M. (2000). Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *Journal of Bone and Mineral Research,* Vol.15, No.4, pp. 721-739, ISSN 8756-3282

Lane, N.E. (2006). Epidemiology, etiology, and diagnosis of osteoporosis. *American Journal of Obstetrics and Gynecology,* Vol.194, Suppl 2, pp. S3-11, ISSN 0002-9378

Lash, R.W.; Nicholson, J.M. Velez, L. van Harrison, R. & McCort, J. (2009). Diagnosis and management of osteoporosis. *Primary Care,* Vol.36, No.1 , pp. 181-198, ISSN 0095-4543

Leib, E.S.; Lewiecki, E.M. Binkley, N. Hamdy, C. & International Society for Clinical Densitometry. (2004). Official positions of the International Society for Clinical Densitometry *Journal of Clinical Densitometry,* Vol.7, No.1, pp. 1-6, ISSN 1094-6950

Lems, W.F. (2007). Clinical relevance of vertebral fractures. Annals of the rheumatic diseases, Vol.66, No.1, pp. 2-4, ISSN 0003-4967

Lewiecki, E.M. & Laster, A.J. (2006). Clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. *The Journal of Clinical Endocrinology and Metabolism,* Vol.91,No.11, pp. 4215-4222, ISSN 0021-972X

Marshall, D.; Johnell, O. & Wedel, H. (1996). Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *British Medical Journal,* Vol.312,No.7041, pp. 1254-1259, ISSN 0959-8138

Mauck, K.F. & Clarke, B.L. (2006). Diagnosis, screening, prevention, and treatment of osteoporosis. *Mayo Clinic Proceedings,* Vol.81, No.5, pp. 662-672, ISSN 0025-6196

Miller PD. (1999). Management of osteoporosis. *Disease-a-month,* Vol.45, No.2, pp. 21-54, ISSN 0011-5029

National Osteoporosis Foundation. (2010). *Clinician's Guide to Prevention and Treatment of Osteoporosis.* National Osteoporosis Foundation, ISBN 978-0-9798989-9-0, Washington (DC)

National Osteoporosis Foundation. (2003). *Physician's guide to prevention and treatment of osteoporosis.* National Osteoporosis Foundation, Washington (DC)

Nguyen, N.D.; Frost, S.A. Center, J.R. Eisman, J.A. & Nguyen, T.V. (2008). Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporosis International,* Vol.19, No.10, pp. 1431-1444, ISSN 0937-941X

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. (2001). Osteoporosis prevention, diagnosis, and therapy. *The Journal of the American Medical Association*, Vol.285, No.6, pp. 785-795, ISSN 0098-7484

Pluijm, S.M.; Koes, B. de Laet, C. Van Schoor, N.M. Kuchuk, N.O. Rivadeneira, F. Mackenbach, J.P. Lips, P. Pols, H.A. & Steyerberg, E.W. (2009). A simple risk score for the assessment of absolute fracture risk in general practice based on two longitudinal studies. *Journal of Bone and Mineral Research*, Vol.24, No.5, pp. 768-774 ISSN 8756-3282

Saag, K.G & Genusens P. (2009). Progress in osteoporosis and fracture prevention: focus on postmenopausal women. *Arthrotis Research & Therapy*, Vol.11, No.5, pp.251, ISSN 1478-6354

Sambrook, P. & Cooper, C. (2006). Osteoporosis. *Lancet*, Vol. 367, No.9527, pp. 2010-2018, ISSN 0140-6736

Schousboe, J.T.; Vokes, T. Broy, S.B. Ferrar, L. McKiernan, F. Roux, C. & Binkley. N. (2008). Vertebral Fracture Assessment: the 2007 ISCD Official Positions. *Journal of Clinical Densitomery*, Vol.11, No.1, pp. 92-108, ISSN 1094-6950

Schuit, S.C.; van der Klift, M. Weel, A.E. de Laet, C.E. Burger, H. Seeman, E. Hofman, A. Uitterlinden, A.G. van Leeuwen, J.P. & Pols, H.A. (2004). Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone*, Vol.34, No.1, pp. 195-202, ISSN 8756-3282

Seibel, M.J. (2005). Biochemical markers of bone turnover: part I: biochemistry and variability. *The Clinical biochemist. Reviews*, Vol.26, No.4, pp. 97-122, ISSN 0159-8090

Siris, E.S.; Chen, Y.T. Abbott, T.A. Barrett-Connor, E. Miller, P.D. Wehren, L.E. & Berger, M.L. (2004). Bone mineral density thresholds for pharmacological interventions to prevent fractures. *Archives of internal medicine*, Vol.164, No.10, pp. 1108-1112, ISSN 0003-9926

Tannenbaum, C.; Clark, J. Schwartzman, K. Wallenstein, S. Lapinski, R. Meier, D. & Luckey, M. (2002). Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *The Journal of Clinical Endocrinology and Metabolism*, Vol.87, No.10, pp.4431-4437, ISSN 0021-972X

Unnanuntana A, Glandnick BP, Donnelly E, Lane JM. The assessment of fracture risk. J Bone Joint Surg Am 2010;92:743-53.

US Preventive Services Task Force. (2002). Screening for osteoporosis in postmenopausal women: recommendations and rationale. Annals of Internal Medicine, Vol.137, No.6, pp. 526-528, ISSN 0003-4819

van Geel, T.A.; van den Bergh, J.P. Dinant, G.J. & Geusens, P.P. (2010). Individualizing fracture risk prediction. *Maturitas*, Vol.65, No.2, pp.143-148, ISSN 0378-5122

van Helden, S.; van Geel, A.C. Geusens, P.P. Kessels, A. Nieuwenhuijzen Kruseman, A.C. & Brink, P.R. (2008). Bone and fall-related fracture risks in women and men with a recent clinical fracture. *The Journal of bone and joint surgery. American volume.* Vol.90, No.2, pp. 241-248, ISSN 0021-9355

van Staa, T.P.; Geusens, P. Pols, H.A. de Laet, C. Leufkens, H.G. & Cooper, C. (2005). A simple score for estimating the long–term risk of fracture in patients using oral glucocorticoids. *Monthly journal of the Association of Physicians.* Vol.98, No.3, pp.191-198, ISSN 1460-2725

WHO Scientific group on the assessment of osteoporosis at primary health care level. (2004). Summary meeting report, July,2011, Available from:
www.who.int/chp/topics/Osteoporosis.pdf

**Osteoporosis**

Edited by PhD. Yannis Dionyssiotis

Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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