review article

Office Practice of Osteoporosis Evaluation

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ABSTRACT

Osteoporosis is a metabolic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Bone fragility depends on bone density, turnover and microarchitectural features, such as relative trabecular volume, spacing, number and connectivity. Previous fragility fractures increase the fracture risk irrespective of bone density. Other risk factors must also be considered as many fractures occur in patients with osteopenia on densitometry. On the other hand, the diagnosis of osteoporosis and increased fracture risk should not be based on densitometric data alone when young populations such as men below 65 years, premenopausal women, adolescents and children are considered. **(Arq Bras Endocrinol Metab 2006;50/4:674-684)**

Keywords: Osteoporosis; Risk factors; Fractures; Densitometry; Bone markers

RESUMO

Avaliação da Osteoporose no Consultório.
Osteoporose é uma doença metabólica caracterizada por redução da massa óssea e deterioração da microarquitetura do tecido ósseo, levando a um aumento da fragilidade do osso e conseqüente aumento no risco de fratura. A fragilidade óssea depende da densidade óssea, do *turnover* e da microarquitetura, com o volume trabecular relativo, espaçamento, número e conectividade. Fraturas de fragilidade prévias aumentam o risco de fratura, independente da densidade óssea. Outros fatores de risco devem também ser considerados, uma vez que muitas fraturas ocorrem em pacientes com osteopenia à densitometria. Por outro lado, o diagnóstico de osteoporose e aumento do risco de fratura não deve basear-se apenas nos dados densitométricos, quando populações jovens, como homens abaixo dos 65 anos, mulheres pré-menopausadas e crianças e adolescentes, são consideradas. **(Arq Bras Endocrinol Metab 2006;50/4:674-684)**

Descritores: Osteoporose; Fatores de risco; Fraturas; Densitometria; Marcadores ósseos

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OSTEOPOROSIS IS DEFINED AS A METABOLIC disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk (1). This definition leads to two main conclusions. First, the concept of bone fragility embraces much more than a simple view of the bone mineral density (BMD). It includes the bone turnover, which can be measured by the biochemical markers; macrostructural characteristics of the bone such as geometry and section modulus; and microarchitectural features, such as relative trabecular volume, trabecular spacing, number and connectivity. Second, any method that

diagnoses osteoporosis must be able to identify fracture risk. The current challenge is how to assess these characteristics and which methods are worth the effort and the cost to be utilized.

CLINICAL FACTORS

There are controversies about which is the best strategy to screening patients for osteoporosis. Some groups recommend selecting patients based on particular risk factors for future fractures (2-5). The first question is which of them is more correlated with a high risk of fracture. The second question is if they have a place in clinical practice as a tool for diagnosis of osteoporosis. To answer these questions some clinical decision rules based on weighted indices of a few major risk factors have been developed to identify postmenopausal women with low BMD, like ORAI (4), SCORE (5), OSIRIS (6) and OST (7) (table 1).

These indices, however, are very simplistic and do not consider many important clinical factors. There is controversy regarding the importance of some clinical factors, as for example coffee drinking, but there is a consensus for others such as female sex, advanced age, white race, fragility fracture in a first-degree relative, personal history of fragility fracture, low body mass index (BMI), current smoking and treatment with systemic glucocorticoids (more than 7.5 mg of

prednisone daily for more than 3 months). Additional risk factors are late menarche, estrogen deficiency at an early age (below 45 yr), poor health/frailty, recent falls, low calcium intake (lifelong), low physical activity, and alcohol in amounts of more than two drinks per day (8-10).

BIOCHEMICAL MARKERS OF BONE TURNOVER

Biochemical bone markers provide information about the dynamic process known as bone turnover. Osteoporosis is always due to an imbalance of this process, with a predominance of bone resorption over bone formation. Several bone markers are available (table 2), but they still lack sensitivity and specificity and must be used with caution in clinical practice (11). The most frequently used are total alkaline phosphatase (AP), bone-specific alkaline phosphatase (BSAP), osteocalcin (OC), and the N- and C- telopeptide of collagen cross-links (NTx and CTx).

Total AP is widely used, but BSAP is more reliable as a bone formation marker, especially in disorders that also increase AP, such as hepatobiliary diseases (11). OC is another non-collagenous protein secreted by osteoblasts, accepted as a marker of bone formation and turnover (12).

Hydroxyproline (Hyp) is not specific of bone collagen, its urinary excretion is influenced by diet, and

Table 1. Characteristics of the clinical decision rules, and the cut-offs for a positive test.

Decision Rule	Characteristics	Points Added to Index	Cut-offs
SCORE	Non-black race	+ 5	Low-risk: ≤ 6
	Rheumatoid arthritis	+ 4	
	Non-traumatic fracture after age 45	+ 4 (per fracture up to a maximum of 12)	Medium risk: 7–15
		+ 1	High risk: ≥ 16
	Never received HRT	3 x result	
	Age (years) / 10	-1 x result	
	Weight (pounds) / 10		
ORAI	Age ≥ 75 years	+ 15	Low-risk: ≤ 8
	Age 65–74 years	+ 9	
	Age 55–64 years	+ 5	Medium risk: 9–17
	Weight < 60 kilograms (Kg)	+ 9	
	Weight 60–69 Kg	+ 3	High risk: ≥ 18
	Not current HRT user	+ 2	Low-risk: ≥ 2
OSIRIS	Weight (Kg)	+ 0,2 x result	Medium risk: -1 to -3
	Age (years)	-0,2 x result	High risk: ≤ -4
	History of low impact	– 2	
	fracture(s)	+ 2	
	HRT		
OST	Weight (Kg)	0,2 x (weight – age)	Low-risk: ≥ 2
	Age (years)		Medium risk: -1 to -3
			High risk: ≤ -4

HRT: hormone replacement therapy for menopause.

its use has been abandoned (11). The development of assays for various collagen breakdown products has increased the clinical use of bone resorption markers. Collagen molecules in the bone matrix are staggered to form fibrils that are joined by covalent cross-links, which consist of hydroxylysyl-pyridinolones (Pyd) and lysil-pyridinolones (deoxypyridinolines: Dpd). Pyd is presented to some extend in type II collagen of cartilage and other connective tissue, whereas Dpd has greater specificity as it is restricted to bone collagen. There are several immunoassays that can measure total and free Pyd and Dpd in urine. In addition, immunoassays are also available for measuring the amino- and carboxy-terminal telopeptides of type I collagen (NTx and CTx), the bone resorption markers that better correlate with bone turnover. All these methods carry the problems of urinary measurements, such as variability in the creatinine excretion and potential artifactual changes due to alteration in muscle mass. For this reason, new clinical assays have been developed for measuring NTx and CTx in blood. Intra- and interassay variability of urine and serum markers is on the order of 20–30% and 10–15%, respectively (12).

Despite the problems about variability, sensitivity and specificity, the biochemical bone markers are important in clinical practice. Variations in blood levels or urinary excretion can identify changes in bone remodeling within a relatively short interval (several days to months) before changes in BMD can be detected (8). That is why the main clinical use of these markers is to monitor the effectiveness of antiresorptive therapy. They can also be used to select patients for treatment with this class of drugs, once patients with the highest levels of bone turnover markers seem to have the best response to antiresorptive therapy (11).

Another important fact is that biochemical bone markers do correlate with fracture risk. In European postmenopausal women included in the EPI-DOS study, high bone resorption markers (CTX, NTX and PYD) were independently associated with a high-er risk of hip fracture, and their combination with low BMD was an even stronger predictor (13,14). In the OFELY study, high levels of AP were an independent risk for fracture (15).

Finally, the interpretation of biochemical bone markers in children and adolescents is problematic, because they lack normality standards. Besides, bone turnover is very high in childhood and puberty due to the state of skeletal growing, which enlarges the physiological variations of these markers (11).

BONE DENSITOMETRY

Bone densitometry is a highly useful quantitative method for assessing skeletal status. The three clinical applications are: a) diagnosis of osteopenia and osteoporosis, b) fracture risk prediction, and c) serial monitoring of BMD to measure response to diseases or medications.

Dual energy X-ray absorptiometry (DXA) is a reliable method, with a reported precision error of about 1% in ideal conditions, and approximately 2% in clinical practice (14). To interpret the results, the BMD obtained is compared to a normal reference population: T-score is the number of standard deviations (SD) in which the patient BMD value differs from that obtained in a healthy young adult population of the same sex (peak bone mass); Z-score is defined as the number of SD above or below the average BMD in age-matched controls of the same sex, race and body mass index.

The definition of osteoporosis by the World Health Organization (WHO) is a BMD 2.5 SD or more below the mean of a young adult, normal reference population (table 3) (16). This classification is based on extensive cross-sectional data in postmenopausal white women showing a consistent correlation between BMD measured by DXA and lifetime fracture risk (9). In fact, BMD is the best way to diagnose osteoporosis, since it is the single best predictor of fracture risk (17). The gradi-

Table 2. Currently available bone biochemical markers (from ref. 12)

Blone Formation Markers	Bone Resorption Markers	
Blood	Blood	Urine
Osteocalcin (OC)	Tartrate-resistant acid phosphatase (TRAP)	Hydroxyproline (Hyp)
Total alkaline phosphatase (AP)		Free and total pyridinolines (Pyd)
Bone-specific alkaline phosphatase (BSAP)	C-telopeptide of procollagen cross-links (CTx)	Free and total deoxypyridinolines (Dpd)
Aminoterminal propeptide of type I collagen (PINP)	N-telopeptide of procollagen cross-links (CTx)	N-telopeptide of collagen cross-links (NTx)
Carboxiterminal propeptide of type I collagen (PICP)	Cross-linked C-telopeptide of type I collagen (ICTP)	C-telopeptide of collagen cross-links (CTx)

ent of fracture risk prediction is approximately 1.5 per SD (9). Each SD reduction in femoral-neck BMD increases the age-adjusted risk of hip fracture by a factor of about 2 (range, 2.0–3.5) and the risk of any non-traumatic fracture by almost the same measure (range, 1.7–2.4). Similarly, each SD reduction in lumbar spine BMD increases the risk of spinal fracture by a factor of about 2.3 (range, 1.9–2.8). Proximal femur BMD appears to be the best overall predictor of fracture risk (14,16,17).

For serial measurements of BMD, it would be ideal if patients were evaluated on the same machine and by the same technician, but this is sometimes difficult in clinical practice. BMD testing for serial monitoring is generally performed each 12 or 24 months.

Despite the recognized utility of bone densitometry, there are controversies about the indications for bone density testing, which sites must be used to measure BMD, and the cut-off for diagnosis of osteoporosis in populations other than postmenopausal women.

Indications for bone density testing

The International Society for Clinical Densitometry (ISCD) published the last position statements regarding these topics (table 4) (9). The indication for BMD testing in all women 65 years or older, recommended by the National Osteoporosis Foundation (NOF) (18) and US Preventive Services Task Forces (19), is contested by the International Osteoporosis Foundation (IOF). This group suggests that only patients with risk factors should be screened with bone densitometry (20). The conflicting position is in part due to the high cost of bone densitometry as the first screening exam and the lack of availability of DXA machines, especially in developing countries, such as Brazil. Lewiecki et al. agree that there are many inconsistencies and uncertainties in the acquisition, analysis and interpretation of the bone density test in clinical practice (21). That is why scientists and health care practitioners are looking for other methods to diagnose osteoporosis and consequently evaluate the fracture risk.

Sites to measure BMD

Discordance among skeletal sites is not surprising, as the composition and metabolism are not uniform along the skeleton. Trabecular or cancellous bone is relatively prominent in the vertebral column, while cortical or compact bone is more abundant in the long-bone shafts of the apendicular skeleton. Since trabecular bone is in intimate contact with the cells of the marrow cavity, it is more influenced by cytokines and consequently by estrogen deficiency and glucocorticoid excess than cortical bone, which is more under control of 1,25-dihydroxyvitamin D_3 and parathyroid hormone (22).

There is some discordance among experts about the best sites to measure BMD. In general, bone mass at peripheral sites correlates with measurements at more central sites, such as hip and spine (r values between 0.6 to 0.7). However, evaluation of BMD only at peripheral sites will miss a substantial number of individuals with osteopenia and osteoporosis. In fact, measurement of the site in question gives the best predictive value of the risk of fracture at that site (16). Since the sites more prone to fracture are spine, femur and distal radius, they are chosen to detect osteoporosis. Forearm BMD should be measured specially when hip and/or spine cannot be measured or interpreted, in cases of hyperparathyroidism, or in very obese patients (over the weight limit for DXA table). According to ISCD, the WHO classification for diagnosis of osteoporosis and osteopenia should not be used for peripheral sites, except distal radius. (9).

Quantitative Ultrasonography (*QUS*) measures bone density in peripheral sites using parameters of ultrasound transmission. QUS is the easiest and the most affordable screening approach, less expensive than DXA, does not use ionizing radiation and the machine can be portable (16). The heel was of particular interest, because its composition, primarily cancellous bone, is similar to that of the spine (16). Although the correlation between QUS and DXA is

Table 3. World Health Organization (WHO) criteria for the diagnosis of osteoporosis based on bone mass or density (from ref. 16).

Category	Criteria (1)
Normal	T-score ≥ -1 SD
Osteopenia	T-score < -1 SD but > -2.5 SD
Osteoporosis	T-score ≤ -2.5
Severe Osteoporosis	T-score ≤ -2.5 and fragility fracture

(1) The T-score to be selected for this criterion is the lowest of posterior-anterior spine, femoral neck, total hip, trochanter, or the 33% radius if measured (ref 9). BMD: Bone mineral density, SD: Standard deviations, T-score: number of standard deviations in which the patient's BMD differs of the value of average peak BMD in young adults.

Table 4. Currently indications for bone density testing, according to ISCD (from ref. 9).

- Women ≥ 65 years
- Postmenopausal women < 65 years with risk factors
- Men ≥ 70 years
- Adults with a fragility fracture
- Adults with a disease or condition associated with low bone mass or bone loss;
- Adults taking medications associated with low bone mass or bone loss
- Anyone being considered for pharmacological therapy
- Anyone being treated, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

modest, prospective studies using QUS of the heel have predicted hip fracture and all non-vertebral fractures nearly as well as DXA at the femoral neck (8). However, the ISCD states that QUS has not yet acquired its place in clinical practice and cannot be applied to quantify bone density or diagnose osteoporosis until device-specific cut-points are established; besides, because of its low reproducibility, it should not be used for monitoring treatment (9,10).

Special populations

There are few guidelines regarding indications for testing populations other than postmenopausal women.

Children and adolescents (before 20 yr)

As children and adolescents have not achieved peak of bone mass, Z-score should be used instead of T-score, using the best available pediatric databases of age- and gender-matched controls. Once the value of BMD to predict fractures in this young group is not clearly determined, and there is no agreement on standards for adjusting BMD for factors such as bone size, pubertal stage, skeletal maturity, and body composition, the appropriate terminology is "low bone density for chronological age" when Z-score is below -2.0 SD (9). As a consequence, the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometry criteria alone.

Premenopausal women

This group is usually not at high risk for fragility fracture, unless there is a secondary cause for osteoporosis or risk factors for fracture. Thus, the diagnosis of osteoporosis in premenopausal women should not be made on the basis of densitometry criteria alone (9). There is controversy about the use of Z-scores rather than T-scores, due to lack of population-based studies (9,20). Although the age-matched Z-score and the young-adult-matched T-score are likely to be identical or very similar in premenopausal white women, discordance between T-scores and Z-scores are expected when there are differences in ethnicity in the reference databases used (9).

Men

Men are less likely to have a fragility fracture, as they have a higher peak bone mass (by about 8–10%), larger area density and muscular mass and they fall less than women. Lifetime risk of fracture in men ranges from 13 to 25%, much lower than estimated for Caucasian women, in whom lifetime fracture risk approaches 50%. Moreover, men tend to develop osteoporosis later in life, by about a decade (23). Besides, the data that underlie the application of BMD measurements in women are much less defined in men (24). The question is which men should have BMD measurements, and how should results be interpreted?

The ISCD states that all men 70 years or older should be directed to bone density testing (table 4). However, other populations of men at high risk of fragile fracture should also be screened, such as those who suffered low trauma fractures, have vertebral deformity, radiographic osteopenia, or conditions recognized to impart risk for bone loss and fractures (24). The ISCD criteria for osteoporosis in men 65 yr and older is a T-score at or below -2.5. Men below 65 yr should only be considered to have osteoporosis if a T-score ≤ -2.5 is associated with other risk factors for fracture or with known causes of secondary osteoporosis. In men under 50 yr, the diagnosis of osteoporosis should not be made on the basis of densitometry criteria alone (9).

RADIOGRAPHS AND MORPHOMETRIC X-RAYS ABSORPTIOMETRY

The decrease in mineralized bone volume results in a decrease of the total bone calcium and absorption of the x-ray beam, a phenomenon known as "increased radiolucency". Thus, radiographic findings suggestive of osteoporosis are frequently encountered in clinical practice, such as cortical thinning, uniform trabecular resorption, widening of medullary space and accentuation of the cortex of vertebrae resulting in the appearance of "picture framing" (25).

As a simple radiograph is not sensitive or capable to distinguish between the different degrees of decreased bone density — therefore it cannot be related to fracture risk — it is not a reliable tool for screening, diagnosis or serial assessment of osteoporosis. Its value is to detect secondary causes of osteoporosis, such as pseudofractures and Looser's zones (focal accumulations of osteoid in compact bone at right angles to the longer axis) in osteomalacia; subchondral bone resorption and "brown tumors" in hyperparathyroidism; or typical osteolytic lesions in multiple myeloma (25).

Another important role for radiographs is to detect lumbar spine alterations that can explain discrepancies in vertebral BMD such as osteophytes, aortic calcification, fracture and Paget's disease — all of them can falsely elevate BMD in the densitometry evaluation. Finally, radiographs can detect complications of osteoporosis, mainly vertebral fractures and deformities (26).

Ascertainment of vertebral fracture is important, because it allows the assessment of bone fragility independent of BMD: a previous vertebral fracture increases the risk of developing a new spine fracture up to 4- to 5-fold (27) and 1,5-fold the risk of future hip fractures (28). Even a patient with normal BMD and a vertebral fracture is at slightly higher risk than a patient with low BMD but no fractures. A patient with low BMD and previous vertebral fracture has a 25-fold higher risk for subsequent fractures than a person without these two features (29). For this reason, the presence of fragility fractures classifies the patient as severe osteoporosis when associated with a low BMD (17) (table 1). Posteroanterior (PA) and lateral spine radiographs are the gold standard methods to detect vertebral fracture. The semiquantitative method of Genant defines criteria to detect vertebral fractures that are used worldwide (30). Any person with osteoporosis that have lost height (more than 4 cm historical height loss; 2 cm prospective height loss in a year) and complains of continuous back pain should be investigated with a lateral spine radiographs (10). The problem is that loss of height is neither sensitive nor specific, and vertebral fractures are not commonly suspected in patients reporting back pain, unless it is associated with trauma, and then may not be considered osteoporotic fractures (non-traumatic). Besides, only 30% of fractures present with back pain. As plain lateral radiographs are not routinely solicited for screening, only about one in four vertebral fractures are clinically recognized (29). Delmas PD et al., in the IMPACT study, observed that underdiagnosis of vertebral fractures is a worldwide problem (31).

Vertebral fracture assessment (*VFA*) is a new technique to detect vertebral fracture, which can be performed just after BMD has been evaluated. Also called "Instant Vertebral Assessment" (IVA) or "Morphometric X-ray Absorptiometry" (MXA), it uses DXA scanners to acquire a lateral image of the lumbar and thoracic spine. It allows a more uniform acquisition procedure, with little or no magnification, smaller effective radiation dose to the patient (100 times lower than conventional radiographs), and a more consistent software guided analysis (29). However, there is less spatial resolution than conventional radiograph, more evident in the upper thoracic vertebrae, due to the superposition of soft tissue, scoliosis, scapulae and rib shadows (32). Lateral spine radiographs are still the gold standard method to detect vertebral fracture, but VFA has a good correlation with plain radiographs and is a useful test to exclude the presence of vertebral fracture due to its high predictive negative value.

BONE BIOPSY

Bone biopsy is an expensive and invasive procedure that involves a small risk of complications (0.7%) such as hematomas, pain, transient neuropathy, wound infection, osteomyelitis and fracture. Besides, confounding diagnosis is usually ruled out by noninvasive clinical methods. For this reason, the number of indications for this procedure is very small. Yet, bone biopsy can help to rule out potential causes not readily apparent, such as occult forms of osteomalacia, osteogenesis imperfecta, mastocytosis, and malignancy (23). In postmenopausal osteoporosis, bone biopsy is restricted to clinical research when histomorphometry is necessary to evaluate the effect of a new anti-osteoporotic treatment (33).

NEW APPROACHES

The concept of bone quality stimulates all scientists to look for new methods to provide structural information about bone. There are clinical questions that cannot be solely explained by BMD, such as why fluoride therapy is ineffective in preventing fractures, despite the enormous increase in BMD; why the decrease in fracture risk obtained with various anti-resorptive drugs is similar, despite the differences in the percent increase in bone density (34); also, why a previous fracture increases the risk for new fractures in patients with the same BMD values. So, BMD is insufficient to

accurately predict fracture risk or to evaluate the effects of an antiosteoporosis drug. This is also true for the anabolic drugs, which not only increase BMD, but also restore trabecular connectivity.

New techniques can also assess macrostructural characteristics of the bone such as geometry and section modulus: quantitative computed tomography (QCT), high resolution computed tomography (hrCT) and high resolution magnetic resonance imaging (hrMR). These are non-invasive methods, which permit serial measurement of almost every body site (35).

To evaluate microarchitectural features, such as relative trabecular volume, trabecular spacing, number and connectivity, it is necessary to use methods like micro-computed tomography (µCT) and micro-magnetic resonance imaging (µMR), which permit highly precise and accurate measurement of bone mechanical features (35).

Macrostructural assessment

QCT allows selective measurements of the trabecular and cortical parts of vertebral bodies as it measures true volumetric density (grams per cm^3), an advantage over DXA, which gives an areal density (grams per cm^2) (36). Besides, since QCT measures cancellous bone of lumbar spine exclusively, it is less likely to detect artifacts of aging such as osteophytes and aortic calcifications, compared to DXA (16). Disadvantages are changes in the bone marrow space with aging, which can interfere with the lumbar spine density measurement by QCT; high cost of the machines and the test; poor availability; higher precision error than DXA; and a higher radiation exposure (16,36). Furthermore, fracture prediction by QCT is as good, but no better than that obtained by DXA (16).

hrMR initially appeared unsuitable for assessing bone. Although hrMR provides no direct information on density, because of positive background given by all types of bone marrow, it provides some resolution of the internal structure of cancellous bone. At present, hrMR investigation of the skeleton remains a research procedure because of its high cost and complexity (35).

Microstructural assessment

µTC can provide images with resolution of less than 10 µ (1–100 µ). Geometric three-dimensional parameters, including the orientation, shape, and connectivity of trabeculae can be assessed, providing important information regarding bone strength. It is helpful for assessing changes in microarchitecture after treatment with antiosteoporosis agents. Besides, analysis using µTC was found to be more useful in identifying

subjects at high risk of fracture than clinical bone density measurements using DXA (37). Unfortunately, its use is still limited to research because it requires invasive biopsy, is expensive, and its equipment is not widely available.

µMR has similar strength and weakness, except for the absence of ionizing radiation, and the greater complexity and expense of this technology (35).

DIFFERENTIAL DIAGNOSIS

The most common cause of low bone mass is involutive osteoporosis, which includes postmenopausal and senile osteoporosis. Secondary osteoporosis must be considered in the following conditions: premenopausal women with unexplained bone loss or a history of a fragility fracture; all men; a Z-score lower than -2.0; clinical or radiological signs of other disease (21,38). Even postmenopausal women should be carefully evaluated, because no signs, symptoms or diagnostic tests are specific for involutive osteoporosis, and this diagnosis must be made by excluding other diseases (39).

The secondary causes for osteoporosis can be organized into several categories: endocrine (hyperparathyroidism, hypogonadism, hyperprolactinemia, hypercortisolemia, hyperthyroidism, acromegaly, late hypopituitarism), gastrointestinal (gastrectomy, celiac disease, Gaucher disease, cholestatic liver disease, inflammatory bowel disease, hemochromatosis, parenteral nutrition), hematological (multiple myeloma, leukemia, lymphoma, mastocytosis), renal (renal tubular acidosis, renal osteodystrophy, hypercalciuria) and connective tissue disorders (osteogenesis imperfecta, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Marfan's syndrome, homocystinuria). Osteomalacia, nutritional deficiencies (vitamin D deficiency or insufficiency, leading to secondary hyperparathyroidism) and drugs (alcohol, glucocorticoids, anticonvulsants, GnRH agonists, excessive T4 doses, heparin, immunosuppressive agents, antiretroviral drugs and lithium) must be considered. Also, a variety of other common and serious chronic systemic disorders such as congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease and acquired immunodeficiency syndrome (AIDS) can cause osteoporosis (8,39-41).

In premenopausal women, more than 50% of the cases are associated with secondary causes, the most common being hypogonadism, thyroid hormone excess, use of glucocorticoids and anticonvulsants (8). Among men, 30% to 60% of osteoporosis cases are

associated with secondary disorders (8). The three major causes of osteoporosis in men are alcohol abuse, glucocorticoid excess, and hypogonadism (8,23). In many series, these three etiologies account for 40–50% of all men with osteoporosis. Even when secondary causes are exhaustively searched, approximately 40–50% of men in most series remain without a defined etiology, a condition known as idiopathic osteoporosis (23).

In children, premature and low-birth weight infants have lower-than expected bone mass in the first few months of life, but the long-term implications are unknown. Cystic fibrosis, celiac disease, and inflammatory bowel disease are examples of conditions associated with malabsorption and osteopenia in some adolescents. Hypogonadal states are relatively common in adolescent girls and young women, especially if there is strenuous athletic training, emotional stress, and low body weight. In anorexia nervosa, hypogonadism and nutrition related factors are critical (11). Pregnancy and lactation usually lead to a transitory decrease in bone density in adult women, but it remains unclear if adolescents also recover from pregnancy-induced bone loss or if they will have limited peak bone mass and will be at a higher risk for osteoporosis later in life (42).

STRATEGY PROPOSAL (figure 1)

The diagnosis of osteoporosis is usually made following a non-traumatic fracture or a DXA exam showing low BMD. Investigation should start with history taking to evaluate all the risk factors and symptoms for possible secondary causes. A physical examination is also essential and it should include an investigation of osteoporosis complications, such as hyperkyphosis, and assessment for loss of height and change in posture (8,38,40).

Another key point is to evaluate the risk of falls, especially in elderly people. This includes a history of circumstances around the fall, drugs, acute or chronic medical problems, and mobility levels; an examination of vision, gait and balance, and function of the leg joints; an examination of basic neurological function, including mental status, muscle strength, peripheral nerves of the legs, proprioception, reflexes, and tests of cortical, extrapyramidal and cerebellar function; assessment of basic cardiovascular status including heart rate and rhythm, postural pulse and blood pressure and, if appropriate, heart rate and blood pressure responses to carotid sinus stimulation. Several conditions increase

the risk of falls: poor postural control; defective propriocepcion; reduced walking speed; weakness of legs; slow reaction time; problems with balance, gait, or mobility; joint disease; impaired cognition or depression, Alzheimer's disease; Parkinson's disease; cerebrovascular disease; peripheral neuropathy; epilepsy; visual impairment; impaired visual acuity; cataracts; glaucoma; retinal degeneration; "blackouts"; hypoglycemia; postural hypotension; cardiac arrhythmia; transient ischemic attack, carotid sinus syncope; and neurocardiogenic (vasovagal) syncope. Besides, extrinsic and environmental factors should also be considered such as inappropriate footwear or clothing, multiple drug therapy; sedatives; hypotensive drugs; hazards indoors or at home: bad lighting; steep stairs, lack of grab rails; slippery floors, loose rugs; pets, grandchildren's toys; cords for telephone and electrical appliances (43). In general clinical practice it is useful to apply the test named "get up and go": elderly people who report a single fall should be observed as they stand up from a chair without using their arms, walk several paces, and return. Those showing no difficulty or unsteadiness need no further assessment (43).

The presence of a key risk factor should alert the physician for the need for further assessment, especially prior fragility fracture, family history of osteoporosis/fragility fracture, and age (10). If there are fracture risk factors or it is suspected that a patient has secondary causes for osteoporosis, the investigation must go on. DXA exam using central measurements — femur and lumbar spine — should be done to diagnose osteoporosis in all situations listed in table 4.

Laboratory testing should be done in all patients with low BMD. The search for secondary causes of osteoporosis is mandatory in men and premenopausal women. However, even postmenopausal women and elderly patients should be carefully evaluated, as the diagnosis of involutive osteoporosis must be made by excluding other diseases (39).

There is no consensus for a cost-effective laboratory evaluation, but the following tests should be considered as a minimum requirement even if there is no other clinical indication: a complete blood count and sedimentation rate velocity to exclude hematological, malignant and connective tissue disorders; routine urinalysis and serum creatinine to exclude renal disorders; serum calcium, phosphate, parathyroid hormone (PTH), and 24-hour urinary calcium, to evaluate bone metabolism (38,40). It is very common in clinical practice, but not a good approach, to initiate calcium and vitamin D supplement to a person with low BMD and/or fragility fracture even before one evaluates serum and
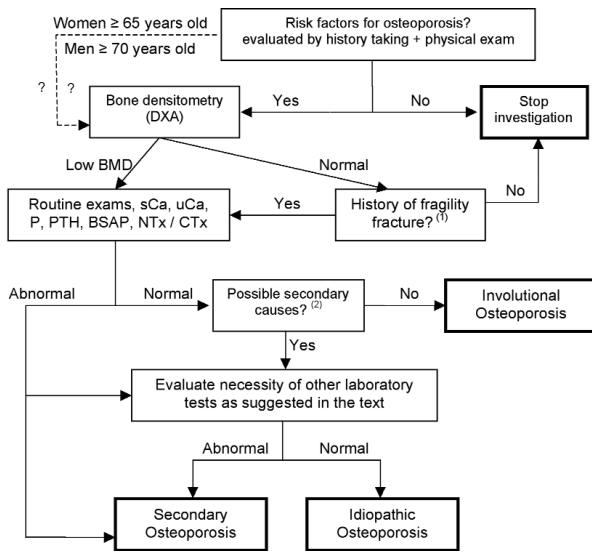
Figure 1. Strategy proposal to diagnosis osteoporosis.
Routine exams: see text, sCa: serum calcium, uCa: 24-hour urine calcium, P: serum phosphate, PTH: parathyroid hormone, BSAP: bone-specific alkaline phosphatase, NTX: N-telopeptide of collagen cross-links, CTX: C-telopeptide of collagen cross-links.
[1] Fragility fracture means fracture with absent or minor trauma
[2] Secondary causes for osteoporosis must be considered in following situations: men; premenopausal women; Z-score ≤ -2.0; diseases or drugs associated with low bone mass or bone loss.

urinary calcium, because these drugs could aggravate pre-existing hypercalcemia or hypercalciuria. 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels have a limited utility for the diagnosis of vitamin D deficiency or insufficiency, due to the many problems with the current assays, the lack of reference methodology and the lack of a clear cut-point, which varies according to populations (44). Vitamin D insufficiency is defined as the lowest threshold value for plasma 25-hydroxyvitamin D that prevents secondary hyperparathyroidism, increased bone turnover and bone loss (45). Thus, high PTH levels associated with low-normal serum and urinary calcium suggest vitamin D insufficiency, a very common situation especially in the elderly (45). On the other hand, the finding of high PTH levels associated with hypercalcemia and high-normal calciuria suggests primary hyperparathyroidism. Finally, the finding of very low serum phosphate in patients with normal PTH leads to the investigation of hypophosphatemic osteomalacia. Bone biochemical markers should also be included as a high turnover helps defining treatment.

If there is any suspicion about specific secondary causes, other laboratory exams should be added: thyroid hormones/TSH, prolactin, gonadotro-

pins and testosterone in men to exclude these endocrinological causes; protein electrophoresis to rule out multiple myeloma; antiendomysial and glutamyl-transpeptidase antibodies for celiac sprue. Obese patients are not supposed to have osteoporosis, and should be screened for Cushing's syndrome.

An important point is that the majority of cases of fracture occur in patients without osteoporosis (15,46). In the OFELY study, among those who developed a fracture, only 44% had osteoporosis, and 48% of those who had fractured had osteopenia (15). Women with osteopenia are at risk for hip fracture especially in the following situations: age higher than 74 years-old (47), prevalent vertebral fracture, lack of exercise, risk of falls, lower total hip BMD and high bone turnover (15,46). So, if your patient is a post-menopausal woman with osteopenia, a careful physical examination must be done to evaluate risk of falls and the possible existence of vertebral fracture in order to define the need for treatment.

Finally, the assessment of vertebral fractures with lateral spine radiographs is mandatory in any person with osteoporosis that has loss of height, hyperkyphosis or continuous back pain, and also when there is history and/or findings suggestive of vertebral fracture not documented by prior radiology study, or commitment to long-term oral or parenteral glucocorticoid therapy (9,10).

CONCLUSION

There are still many controversies about the best way to screen a population for osteoporosis, especially considering the economic and specific aspects of a given population. The currently available methods to evaluate the different aspects of bone quality — BMD, bone turnover, macro and microstructural characteristics — still have strong limitations and none has an ideal correlation with fracture risk. Therefore the strategies proposed, including the one we present, are based on experts' opinions. As a burden of osteoporosis worldwide is predicted, physicians, researchers and governments all over the world should make efforts to implement the current methods and look for new ones to screen and diagnose osteoporosis on a cost/benefit basis.

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