Osteoporosis Diagnosis

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Osteoporosis is a systemic disease characterized by decreased bone strength and an increased risk of fracture. Bone strength progressively declines with aging, and therefore osteoporosis is considered an inevitable process and is not approached as a relevant clinical problem. However, several intervening factors may accelerate this involutional process. One of the major reasons is that osteoporosis is asymptomatic until a fracture occurs, and therefore both the physician and the patients fail to appreciate its importance. As a matter of fact, many patients with osteoporosis and/or at increased risk of fracture are still underdiagnosed and undertreated.

Patients with known or suspected osteoporosis should undergo a through medical history and physical examination to discover risk factors that may have influenced bone accrual and peak bone mass and increased bone fragility (Table 3.1).

3.1 Clinical Evaluation

Individuals with known or suspected osteoporosis should be evaluated for several risk factors (modifiable or not), which can help estimate the individual peak bone mass and bone loss. At the initial visit, administering specific questionnaires could also be useful, but an accurate anamnesis and physical examination can be sufficient.

Questions about the following issues should be asked to help making the correct diagnosis and choose the management of patients with osteoporosis. The most important osteoporosis risk factors are summarized in Table 3.1.

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Table 3.1 Major risk factors of osteoporosis

• Genetic factor
• Environmental factors
–Alcohol abuse
–Cigarette smoking
–Physical inactivity and immobilization
–Low body weight and diet
–Limited exposure to sunlight
• Reproductive history and puberty
• Personal history of fractures and falls
• Drug therapy
• Comorbidities

3.1.1 Genetic Factors

Up to 80% of peak bone mass, depending on the skeletal site, is genetically determined: relevant factors are gender, race, and family history. A maternal history of hip fracture is particularly significant in increasing the fracture risk, but information about other fragility fractures and low BMD in first-degree and other relatives should also be collected [1]. The pathogenesis of osteoporosis is multifactorial, and only a few genes influencing bone mass have been identified (see Chap. 3). Moreover, some genetic diseases associated with osteoporosis, like "osteogenesis imperfecta," particularly late-onset variants, may present with vertebral fractures. Clue for the diagnosis is the family history or specific signs (blue sclerae, lax skin, hypermobile joints, deafness, and cardiac diseases).

3.1.2 Environmental Factors

3.1.2.1 Alcohol

Alcohol abuse (>14 g/day ethanol for women and >28 g/day ethanol for men) is associated with decreased BMD and increased fracture risk, the possible causal relationship being a direct suppression of osteoblasts by alcohol. Moderate to heavy alcohol consumption was also shown to be associated with changes in bone geometry, density, and microarchitecture, which affect bone quality [2]. On the other hand, some studies showed a favorable effect of small daily quantities of alcohol on the bone [3].

3.1.2.2 Cigarette Smoking

Smoking is another risk factor for bone loss. A higher the prevalence of osteoporosis is higher in smokers than in non-smokers, an increased risk of osteoporotic fractures has been shown in the former [4]. Recent studies have shown that smoking leads to a reduced bone resistance to mechanical stress because of deleterious microarchitectural changes in trabecular bone. Finally, cigarette smoking decreases estrogen levels and has influence on body weight [5].

3.1.2.3 Physical Inactivity and Immobilization

Gravity stimulates bone formation, and weight-bearing physical activity has a positive effect on bone mass, but it is difficult to document that exercise can increase bone density in adults. It is well known that athletes have high bone mass, but excessive exercise may also cause bone loss (marathon runners). On the other hand, periods of prolonged bed rest and immobilization due to neurological diseases led to rapid bone loss that can be reversible only in young patients.

3.1.2.4 Low Body Weight and Diet

Nutritional history should be evaluated, since thin habitus is a risk factor for low BMD and fractures. Caloric insufficiency during adolescence is associated with low peak bone mass and loss of weight at any age with bone loss. Inadequate calcium intake in the adolescence adversely affects peak bone mass and may contribute to age-related bone loss, particularly when accompanied by vitamin D deficiency. Conversely diets rich in sodium and animal proteins are associated with hypercalciuria and bone loss [6].

3.1.2.5 Limited Exposure to Ultraviolet Light

Ultraviolet light stimulates vitamin D production in the skin, mostly through sun exposure. Vitamin D insufficiency is rather common and is associated with decreased calcium absorption, subsequent secondary hyperparathyroidism, and bone loss. Long-standing severe vitamin D deficiency may result in osteomalacia.

3.1.3 Reproductive History and Puberty

The age of puberty affects bone mass both in males and females. Indeed, individuals with late pubertal development do not reach the adequate peak bone mass. In women, every condition characterized by a reduction in estrogen levels can be associated with bone loss: irregular menses, history of infertility, and prolonged uses of progesterone contraception [7]. Early menopause (before 45 years) is invariably associated with an increased risk of fractures, but particular attention should be paid to exclude concomitant secondary causes also in this setting. In men history of infertility, loss of libido, and sexual dysfunctions may suggest the presence of hypogonadism and suboptimal exposure of the bone to testosterone. Anorexia nervosa is a good example of a disease that can deeply influence pubertal development and the peak bone mass in both sexes, with a complex pathogenesis due to a combination of endocrine dysfunctions and nutritional deficit [8].

3.1.4 Personal History of Fractures and Falls

This aspect should be carefully investigated, particularly in elderly individuals. Of particular importance is to investigate the circumstances in which a fracture occurred, in order to identify the true “low-trauma, fragility fractures,” namely, those related to

a bone trauma, which should not cause a fracture in a healthy bone (i.e., a fall for the standing position). The hip, spine, and forearm are typically osteoporotic. In the position statement from the National Bone Health Alliance Working Group published in 2014, there was a consensus that the diagnosis of osteoporosis could be established in individuals who experienced a low-trauma hip fracture even without a BMD measurement and in those with osteopenia and a low-trauma clinical vertebral, proximal humerus, or pelvis fractures [9]. The position statement also indicated that a low-trauma distal forearm fracture in a patient with osteopenia at the lumbar spine or hip should be sufficient for the diagnosis of osteoporosis. Vertebral fractures directly reflect bone fragility and predict future new fractures. However, the large majority of spine fractures are not clinically evident, and imaging study can help to identify even old fractures: the incidental finding of a nontraumatic vertebral fracture on a radiograph (morphometric vertebral fracture) may also be considered as diagnostic of osteoporosis [10]. Fractures other than the spine, hip, or forearm should also be evaluated, since virtually all fractures are the results of bone strength and force applied on that bone and therefore could reflect bone fragility and osteoporosis [11].

Information of falls should also be collected, since most fractures are cause by falls. Fall prevention should also be included in an appropriate strategy of fracture prevention. A recent consensus statement recommends asking the patient the following question: "In the past month, have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?" [12]. Indeed, fractures related to falls can be considered a major health problem: one third of people over 65 years falls once each year, and 5% of falls eventually leads to fractures, with subsequent increased mortality, morbidity, and costs for the community. Recent studies have shown the efficacy of physical exercise training as a program of fall prevention in elderly osteoporotic patients [13].

3.1.5 Drug Therapy

Osteoporosis is an adverse effect of many pharmacologic agents, like glucocorticoids, proton pump inhibitors, selective serotonin receptor inhibitors, thiazolidinediones, anticonvulsants, medroxyprogesterone acetate, aromatase inhibitors, heparin, calcineurin inhibitors, androgen deprivation therapy, and some chemotherapies. Glucocorticoid therapy is the most common cause of secondary osteoporosis and is associated with an increased rate of fractures, morbidity, and mortality. Glucocorticoids induce a rapid bone loss, and the fracture risks are already evident within 6 months of therapy, and several studies have shown that bone loss and fracture risk increase with the dose and duration of therapy [14]. The negative effects on bone are multifactorial, and not all of them can be explained by the reduction of BMD. They include direct effects like inhibition of osteoblast function, increased osteoblast and osteocyte apoptosis, and stimulation of the osteoclast, resulting in bone remodeling defects, bone loss, and a fracture risk [15]. Moreover, indirect effects (hypogonadism, kidney calcium loss, low levels of vitamin D) play a role [14]. Antiepileptic drugs, like phenobarbital and phenytoin, interfere with vitamin D metabolism and can cause osteomalacia, secondary hyperparathyroidism, and osteoporosis. Some anticoagulant drugs are known to interfere

with bone density: long-term administration of unfractionated heparin is associated with an increased fracture risk, whereas no data are available on low molecular weight heparin; chronic use of warfarin, which interferes with γ-carboxylation of bone proteins, is associated with an increased risk of fractures [16]. Cyclosporin therapy in transplanted patients is associated with a 10–34% increase in clinical fractures particularly in the first year of treatment [17]. Finally, excessive administration of thyroxin can cause bone loss, particularly in postmenopausal women.

3.1.6 Comorbidities

Several diseases are known to have a deleterious effect on bone and may cause bone loss. Malabsorption syndromes like coeliac disease, peptic ulcer, gastrointestinal inflammatory diseases, chronic liver diseases, and chronic obstructive pulmonary disease can have negative effects on the bone by a combination of factors: excessive cytokine production, nutritional deficiency, decreased physical inactivity, and chronic drug use. The direct effects of cytokines on osteoblast and osteoclast activity and the use corticosteroid therapy can explain why rheumatologic diseases are associated with low BMD and increased fracture risk. Finally, some endocrine disorders cause osteoporosis: primary hyperparathyroidism, thyrotoxicosis, Cushing's syndrome, Addison syndrome, hypogonadism, and type 1 diabetes mellitus. Type 2 diabetes even if usually associated with normal or even increased BMD is also associated with an increased fracture rate [18], which seems to be mediated by the negative effect of advanced glycation end products on bone quality [19].

3.1.7 Physical Examination

Medical history should always be completed with an accurate physical examination. A high loss >4 cm compared with young age or >2 cm from the last visit may suggest a prior vertebral fracture. Thoracic kyphosis, even if it is not diagnostic, can be indicative of the presence of vertebral fractures. Finally, frailty and fall risk should be evaluated by inspection of muscle mass and direct strength testing and gait and stability when the patient is standing.

3.1.8 Algorithms

Fracture risk assessment has been evaluated for many years by BMD, on the basis of the inverse relationship between BMD and fractures. Despite high specificity, this method has low sensitivity since many fractures occur in individuals with osteopenia and several clinical risk factors for fractures are independent from BMD. For this reason, some algorithms based on clinical parameters with and without BMD values have been proposed and now accepted by international guidelines. FRAX is a World Health Organization-sponsored algorithm introduced in 2008 and endorsed by the US National Osteoporosis Foundation (NOF) and other national and

international guidelines for osteoporosis management [20]. It is based on well-validated and weighted clinical risk factors for fracture and can predict hip, spine, humerus, and forearm fractures in males and women aged between 40 and 90 years. It was elaborated on data collected in large prospective studies and subsequently validated in a cohort of more than 230,000 patients.

The 2015 position statement from the National Bone Health Alliance Working Group for clinical diagnosis of osteoporosis agreed that a probability of hip fracture ≥3% or of major osteoporotic fracture ≥20% calculated with FRAX could be considered as an appropriate treatment intervention threshold, as suggested in US NOF Clinician's Guidelines, and could also be used as cutoff for the diagnosis of osteoporosis [9]. There is still an on-going debate in literature regarding the real utility of FRAX and the need of further improvement to the algorithm. Some strengths and limits of FRAX have been recognized. FRAX is free and easily accessible to clinicians and is particularly useful to identify old women with high fracture risk, still untreated. Moreover, it can help in reducing overtreatment in young postmenopausal women, with low BMD and low fracture risk. One possible limit of FRAX is that vertebral fractures have the same value of other fractures in the algorithm, leading to a possible underestimation of fracture risk. Another limit is the age cutoff: the NOF suggests that FRAX should be used for a target age between 50 and 90 years, excluding risk assessment in young people. Moreover, epidemiologic data on which FRAX is based upon were proven in Caucasian women, and few data were available in man and other races. Another limitation of the algorithm is that it does not take into account the dose and duration of glucocorticoid drug therapy. It should be underlined that in the large majority of studies that evaluated osteoporosis treatment efficacy, eligibility criteria were based on BMD and not on FRAX. In conclusion, FRAX algorithm is a valuable and well-recognized tool in the evaluation of fracture risk in osteoporotic patients, but the final decision and treatment threshold should also take into account the clinician experience and judgment.

Other algorithms different from FRAX have been created: in the UK, the National Institute for Health and Care Excellence (NICE) recognizes both FRAX and Qfracture that includes also alcohol, smoking, and falls in the risk assessment [21]. In Italy, an algorithm called DeFRA (an algorithm derived from FRAX and based on fracture risk in Italian population) has been proposed, which includes the same continuous variable of FRAX (age, BMI, BMD) but a more detailed evaluation of other clinical factors (site and number of previous fractures, vertebral BMD in addition to hip BMD, other comorbidities) and more accurate informations on dichotomous variables (smoking, corticosteroid dose, alcohol units) [22].

3.2 Laboratory Testing

No specific biochemical abnormalities are present in patients with involutional osteoporosis. However, biochemical testing may be of help in several instances: (1) uncover metabolic bone diseases which may be associated with clinical features and bone imaging (BMD and X-ray) similar to those typical of osteoporosis, (2) identify

secondary causes of osteoporosis and choice of therapy, and (4) evaluate adherence to therapy.

Secondary causes are found in about 60% of men and 50% of premenopausal women with osteoporosis. Thus an underlying disorder should be searched in all men and premenopausal women with low bone mass. In postmenopausal women secondary causes of osteoporosis are less frequent (20–30% of cases). How extensive the search for secondary causes of osteoporosis should be based on medical history and clinical examination.

The most common causes of secondary osteoporosis are reported in Table 3.2. Most of these conditions may be clinically unapparent and may be discovered only by laboratory testing. The initial evaluation should include the first level tests that, if normal, would exclude other metabolic bone diseases or secondary cause of osteoporosis in about 90% of cases (Table 3.3). An increase of erythrocyte sedimentation rate associated with anemia and an abnormal electrophoretic pattern may suggest the diagnosis of multiple myeloma, which can be confirmed by the finding of elevated light chains at immunoelectrophoretic of serum or urine. A high 24-h urinary calcium excretion (>250 mg in women and >300 in men) in the presence of normal serum calcium may rise the suspicion of idiopathic hypercalciuria, a disorder found in approximately 10% of the general population. Conversely a low 24-h urinary calcium vitamin D deficiency of a malabsorptive state can be suspected. An isolated increase of alkaline phosphatase (especially the bone isoform) with normal levels of other liver enzymes is highly indicative of Paget's disease.

In selected cases, addition tests (Table 3.3, second level) are justified and should be selected on the basis of medical history and clinical examination. For instance, serum PTH should be assayed for the differential diagnosis of hypercalcemia. Serum cortisol should be measured in all cases of unexplained osteoporosis, particularly men, to rule out Cushing's disease. Anti-transglutaminase antibodies

Table 3.2 Most common secondary causes of low bone mass or osteoporosis

Male hypogonadism
Vitamin D deficiency
Malabsorption (especially celiac disease)
Primary hyperparathyroidism
Thyrotoxicosis
Multiple myeloma
Chronic liver diseases
Chronic obstructive pulmonary diseases
Rheumatoid arthritis
Idiopathic hypercalciuria
Solid organ transplantation
Alcohol abuse
Cigarette smoking
Physical inactivity and immobilization
Osteogenesis imperfecta
Anorexia nervosa
Drugs (glucocorticoids, antiepileptic drugs, excessive thyroxin and hydrocortisone replacement therapy)

Table 3.3 Laboratory tests to exclude/identify secondary causes of osteoporosis

First level
• Erythrocyte sedimentation rate
• Full blood count
• Albumin-corrected serum calcium
• Serum phosphate
• Serum alkaline phosphatase
• Protein electrophoresis
• Serum creatinine
• Serum testosterone in males[1] (preferably together with sex-hormone binging protein)
• 24/h urinary calcium[2]
Second level
• Ionized calcium
• TSH
• PTH
• 25OHD
• Morning cortisol after administration overnight of 1 mg dexamethasone
• Anti-transglutaminase antibodies (IgA)
• Tryptase

[1]Preferably together with sex-hormone binging globulin measuremnet, to calculate the free-androgen index

[2]Calcium supplement, if taken by the patient, should be stopped for 2 weeks before urine collection

should be measured in addition to serum 25OHD when urinary calcium excretion is low or in premenopausal women with low bone mass or postmenopausal women with osteoporosis. Once the diagnostic workup is completed, it is prudent to measure serum 25OHD to determine the vitamin D status and, if deficient, guide supplementation in order to reach adequate value.

Several markers of bone turnover (BTM) are currently available, reflecting the process of bone resorption and bone formation [23]. The most widely used are serum C-telopeptide of type 1 collagen (CTX) and urinary deoxypyridinoline for resorption and serum alkaline phosphatase (bone isoform) and procollagen type 1 aminoterminal propeptide (P1NP) for formation. Measurement of BTM has limited, if any, diagnostic value. In adults, an increase of BMT may suggest an accelerated bone loss or other bone disorders (osteomalacia, Paget's disease, bone metastases). Measurement of BTM may provide information that is complementary to BMD measurement. Indeed, high levels of bone resorption markers predict fracture independent of BMD [24] and may suggest pharmacologic therapy even if BMD is not sufficiently low. High levels of bone resorption markers may also predict a benefit of antiresorptive therapy, whereas low levels may suggest continued monitoring. The most valuable use of bone markers is to monitor therapy and check whether patient's adherence to pharmacologic therapy is adequate. Indeed, measurement of either bone resorption or bone formations marks at baseline and 3 months after the institution of therapy. Indeed, if a significant decrease is detected, the treatment can continue. Conversely, if no decrease is found, it will be important to reassess the

patient to identify problems with the treatment [25]. In addition, BTM measurement may be used for assessing the response to therapy. Indeed, compared to BMD, a shorter time (3–6 months) is needed in each patient to evaluate the efficacy of both antiresorptive and anabolic therapies.

3.3 Bone Imaging

The main role of bone imaging in osteoporosis is the detection of vertebral fractures (VF). As a matter of fact, identification of VF is clinically relevant both in terms of further fracture risk, independent of other risk factors, and to select patients for anti-osteoporosis therapy.

Osteoporosis does not cause pain in the absence of fractures, but VF may also be asymptomatic, particularly in patients taking glucocorticoids. Back pain due VF has some typical features. It usually follows a fall or when some strain is applied to the back, such as lifting a suitcase or working in the garden. Loss of height and the finding of kyphosis at clinical examination, even in an asymptomatic patient, may suggest the presence of VF.

Indication for VF assessment therefore includes the presence of symptoms or signs suggestive of vertebral fractures and, in the absence of symptoms, other indications, which include previous fragility fractures and glucocorticoid treatment for more than 3 months using a daily dose of >5 mg daily of prednisone or equivalents (Table 3.3). Finally the search for VF is appropriate in all women aged >70 years and men between 70 and 79 years if T score is <−1.5 and in postmenopausal women and men with specific risk factors.

Spine images can be obtained using plain radiographs of the thoracic and lumbar spine in anteroposterior and, especially, lateral positions or by DXA, using the vertebral fracture assessment (VFA) software program provided with some densitometry devices. The advantage of FVA is the low radiation exposure (3 vs 600 μSv for a lateral lumbar spine X-ray) [26]. When VF are initially detected with VFA in patients in whom conditions other than osteoporosis are suspected, conventional X-ray of the spine should be performed and second-line imaging techniques (CT or MRI) be considered.

Table 3.4 Indication for vertebral fracture testing

• Suggestive symptoms (i.e., back pain that worsen with standing) and signs (i.e., kyphosis)
• Asymptomatic cases:
–All women aged >70 years and men between 70 and 79 years if T score is <−1.5
–Postmenopausal women and men aged 50 years or older with specific risk factors:
Previous fragility fractures
A high loss >4 cm compared with young age or >2 cm from the last visit
Marked reduction of BMD values (T score < −3)
Glucocorticoid therapy with >5 mg daily of prednisone or equivalents for >3 months
Comorbidities associated with increased risk of vertebral fractures *per se*

3.3.1 Conventional X-ray of the Spine

Lateral radiograph alone is often taken, but the anteroposterior images may help to identify the level of vertebral deformity and exclude other causes (i.e., absence of pedicles suggests malignancy).

Three types of vertebral deformities may be detected: wedge, end plate (biconcave if both plates are involved), and crush [27]. The method most commonly used to evaluate VF is based on the semiquantitative method devised by Genant [28]. This method is based on a visual inspection of the lateral spine images, and three deformity grades are defined: (1) mild or grade 1 (approximately 20–25% reduction in the anterior, middle (compared with the posterior height), and/or posterior height and a 10–20% reduction in area), (2) moderate or grade 2 (25–40% reduction in any height and a 20–40% reduction in area), and (3) severe or grade 3 (>40% reduction in any height and area) (Fig. 3.1).

Some vertebral deformities mimic fractures, as in Scheuermann's disease, a self-limiting skeletal disorder of children in which vertebrae grow unevenly resulting in a wedge shape of the vertebrae, causing kyphosis. Malignancy can also cause vertebral deformity, but in this case, erosion of the pedicle, a feature not found in osteoporotic vertebral deformity, is typically present. Paget's disease may affect the spine: the vertebral body may be enlarged, and the bone appears sclerotic with a

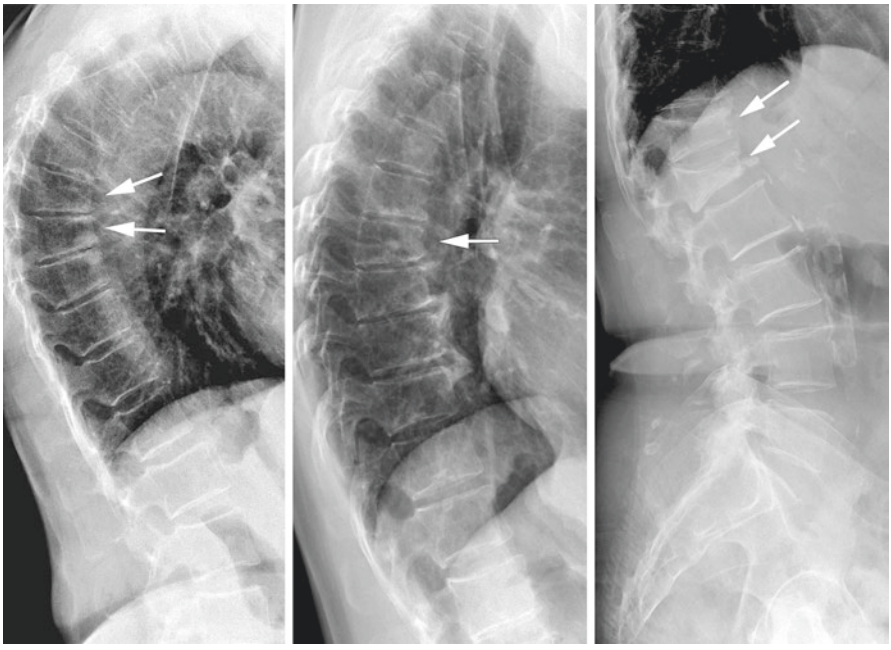

Fig. 3.1 Lateral X-rays of the spine showing a mild (left), moderate (middle), and severe (right) vertebral deformities (with the courtesy of Dr. Daniele Diacinti, University of Rome "La Sapienza," Rome, Italy)

disorganized texture appearance. Osteomalacia may cause vertebral deformities, often involving adjacent vertebrae, with atypical ground-glass appearance. Vertebral plates are deformed with a biconcave appearance (cod-fish appearance).

Vertebral morphometry is a quantitative method of diagnosis of VF based on the measure of anterior, middle, and posterior vertebral heights. It should always follow a qualitative analysis of the spine X-ray. It is performed by a six-point approach, corresponding to the four corners of the vertebral body and the midpoints of the end plate, by which the anterior, middle, and posterior heights are measured from T4 to L5. Several approaches have been proposed to quantify the shape of a vertebral body, based upon the anterior-posterior ratio, middle-posterior ratio, and posterior-posterior adjacent ratio. The algorithm developed by Eastell et al. defines a vertebral fracture if any of the ratio falls 3 SD below the sex- and vertebra-specific mean ratio in normal [29]. A more complex algorithm has been proposed by McCloskey et al. based on the reduction in the ratios, as in Eastell's algorithm, as well as a reduction in the ratios calculated with the "predicted posterior height" [30].

As mentioned before vertebral morphometry can be also performed on images obtained from DXA (VFA) (see chapter "New technologies for skeletal evaluation).

References

1. Bonjour JP, Chevalley T. Pubertal timing, bone acquisition, and risk of fracture throughout life. Endocr Rev. 2014;35(5):820–47. https://doi.org/10.1210/er.2014-1007.
2. Gaddini GW, Turner RT, Grant KA, Iwaniec UT. Alcohol: a simple nutrient with complex actions on bone in the adult skeleton. Alcohol Clin Exp Res. 2016;40(4):657–71. https://doi.org/10.1111/acer.13000.
3. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A. Alcohol intake as a risk factor for fracture. Osteoporos Int. 2005;16(7):737–42. https://doi.org/10.1007/s00198-004-1734-y.
4. Bijelic R, Milicevic S, Balaban J. Risk factors for osteoporosis in postmenopausal women. Med Arch. 2017;71(1):25–8. https://doi.org/10.5455/medarh.2017.71.25-28.
5. Brook JS, Balka EB, Zhang C. The smoking patterns of women in their forties: their relationship to later osteoporosis. Psychol Rep. 2012;110(2):351–62. https://doi.org/10.2466/13.18.PR0.110.2.351-362.
6. Pietschmann F, Breslau NA, Pak CY. Reduced vertebral bone density in hypercalciuric nephrolithiasis. J Bone Miner Res. 1992;7(12):1383–8. https://doi.org/10.1002/jbmr.5650071205.
7. Kaunitz AM, Arias R, McClung M. Bone density recovery after depot medroxyprogesterone acetate injectable contraception use. Contraception. 2008;77(2):67–76. https://doi.org/10.1016/j.contraception.2007.10.005.
8. Thornton D, Gordon CM. Restrictive eating disorders and skeletal health in adolescent girls and young women. Calcif Tissue Int. 2017;100(5):449–60. https://doi.org/10.1007/s00223-016-0164-0.
9. Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, Harris ST, Jan de Beur SM, Khosla S, Lane NE, Lindsay R, Nana AD, Orwoll ES, Saag K, Silverman S, Watts NB. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int. 2014;25(5):1439–43. https://doi.org/10.1007/s00198-014-2655-z.
10. Melton LJ, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. Osteoporos Int. 1999;10(3):214–21.

11. Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, Hillier TA, Lewis CE, Barrett-Connor E, Cummings SR, Study of Osteoporotic F, Osteoporotic Fractures in Men Study Research G. High-trauma fractures and low bone mineral density in older women and men. JAMA. 2007;298(20):2381–8. https://doi.org/10.1001/jama.298.20.2381.
12. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;9:CD007146. https://doi.org/10.1002/14651858.CD007146.pub3.
13. Smulders E, Weerdesteyn V, Groen BE, Duysens J, Eijsbouts A, Laan R, van Lankveld W. Efficacy of a short multidisciplinary falls prevention program for elderly persons with osteoporosis and a fall history: a randomized controlled trial. Arch Phys Med Rehabil. 2010;91(11):1705–11. https://doi.org/10.1016/j.apmr.2010.08.004.
14. Compston J. Clinical question: what is the best approach to managing glucocorticoid-induced osteoporosis? Clin Endocrinol. 2011;74(5):547–50. https://doi.org/10.1111/j.1365-2265.2011.03994.x.
15. Paggiosi MA, Peel NF, Eastell R. The impact of glucocorticoid therapy on trabecular bone score in older women. Osteoporos Int. 2015;26(6):1773–80. https://doi.org/10.1007/s00198-015-3078-1.
16. Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. Ther Adv Musculoskelet Dis. 2014;6(5):185–202. https://doi.org/10.1177/1759720X14546350.
17. Tufano A, Coppola A, Contaldi P, Franchini M, Minno GD. Oral anticoagulant drugs and the risk of osteoporosis: new anticoagulants better than old? Semin Thromb Hemost. 2015;41(4):382–8. https://doi.org/10.1055/s-0034-1543999.
18. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. Osteoporos Int. 2007;18(4):427–44. https://doi.org/10.1007/s00198-006-0253-4.
19. Yamagishi S, Maeda S, Matsui T, Ueda S, Fukami K, Okuda S. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. Biochim Biophys Acta. 2012;1820(5):663–71. https://doi.org/10.1016/j.bbagen.2011.03.014.
20. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, Cauley JA, Compston JE, Dawson-Hughes B, El-Hajj Fuleihan G, Johansson H, Leslie WD, Lewiecki EM, Luckey M, Oden A, Papapoulos SE, Poiana C, Rizzoli R, Wahl DA, McCloskey EV, Task Force of the FI. Interpretation and use of FRAX in clinical practice. Osteoporos Int. 2011;22(9):2395–411. https://doi.org/10.1007/s00198-011-1713-z.
21. Compston J. Osteoporosis: advances in risk assessment and management. Clin Med. 2016;16(Suppl 6):s121–4. https://doi.org/10.7861/clinmedicine.16-6-s121.
22. Adami S, Bianchi G, Brandi ML, Di Munno O, Frediani B, Gatti D, Giannini S, Girasole G, Minisola G, Minisola S, Nuti R, Pedrazzoni M, Rossini M, Varenna M. Validation and further development of the WHO 10-year fracture risk assessment tool in Italian postmenopausal women: project rationale and description. Clin Exp Rheumatol. 2010;28(4):561–70.
23. Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. Nat Rev Rheumatol. 2012;8(7):379–89. https://doi.org/10.1038/nrrheum.2012.86.
24. Garnero P, Shih WJ, Gineyts E, Karpf DB, Delmas PD. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. J Clin Endocrinol Metab. 1994;79(6):1693–700. https://doi.org/10.1210/jcem.79.6.7989477.
25. Diez-Perez A, Naylor KE, Abrahamsen B, Agnusdei D, Brandi ML, Cooper C, Dennison E, Eriksen EF, Gold DT, Guanabens N, Hadji P, Hiligsmann M, Horne R, Josse R, Kanis JA, Obermayer-Pietsch B, Prieto-Alhambra D, Reginster JY, Rizzoli R, Silverman S, Zillikens MC, Eastell R, Adherence Working Group of the International Osteoporosis F, the European Calcified Tissue S. International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates. Osteoporos Int. 2017;28(3):767–74. https://doi.org/10.1007/s00198-017-3906-6.

26. Lewiecki EM, Laster AJ. Clinical review: clinical applications of vertebral fracture assessment by dual-energy X-ray absorptiometry. J Clin Endocrinol Metab. 2006;91(11):4215–22. https://doi.org/10.1210/jc.2006-1178.
27. Jiang G, Eastell R, Barrington NA, Ferrar L. Comparison of methods for the visual identification of prevalent vertebral fracture in osteoporosis. Osteoporos Int. 2004;15(11):887–96. https://doi.org/10.1007/s00198-004-1626-1.
28. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8(9):1137–48. https://doi.org/10.1002/jbmr.5650080915.
29. Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton LJ. Classification of vertebral fractures. J Bone Miner Res. 1991;6(3):207–15. https://doi.org/10.1002/jbmr.5650060302.
30. McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaran S, Kanis JA. The assessment of vertebral deformity: a method for use in population studies and clinical trials. Osteoporos Int. 1993;3(3):138–47.