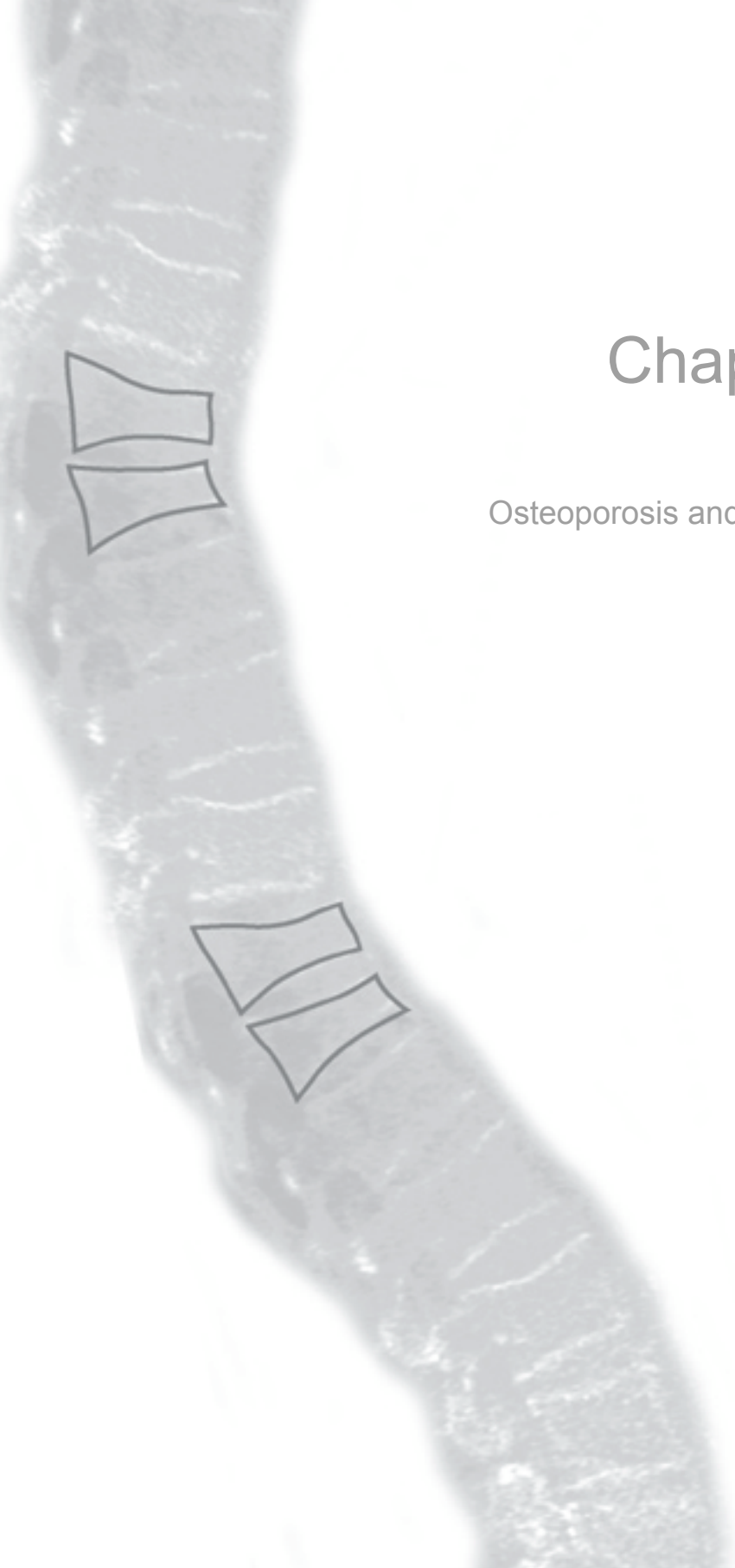

Chapter 2

Osteoporosis and fracture risk: an overview

Definition

Osteoporosis is a skeletal disease characterized by low bone mass and micro architectural deterioration resulting in increased bone fragility and hence susceptibility to fracture.[1] It is a major health problem because of its consequent morbidity, mortality and health-care costs. In 1994, an expert panel convened by the World Health Organization (WHO) formulated an operational definition of the disease for postmenopausal women based on bone mineral density (BMD).[2] BMD can be expressed as a T-score, the value used for diagnosis of osteoporosis, which is a score for the standard deviation (SD) above or below the mean value of peak bone mass in young adults. In addition, a Z-score is used to compare the patient's BMD to a population of peers (SD from the mean BMD of an age-, ethnicity-, and sex-matched reference population). In the WHO definition osteoporosis is defined as a T-score of ≤ -2.5 and osteopenia as a T-score between -1 and -2.5. (Table 2.1).

Table 2.1 Diagnostic criteria for osteoporosis

T-score value	Diagnosis
Above -1.0	Normal bone
Below -1.0 and above -2.5	Osteopenia
Below -2.5	Osteoporosis
Below -2.5 and at least one fragility fracture	Established osteoporosis

This definition of osteoporosis has several limitations. The fracture risk increases with decreasing BMD (gradient of risk) and these cut-offs are somewhat arbitrary. In addition, this definition was established for postmenopausal Caucasian women and may not be applicable to men or premenopausal women and people from other ethnic groups. Besides this, fractures occur in persons without osteoporosis implicating that bone density is not the only determinant of bone's resistance to fracture. It is nowadays well recognized that in particular in minimal trauma fractures bone fragility can be due to reduced bone mass as well as changes in the matrix composition and microarchitecture of bone. In support of this view, a recent consensus conference has defined osteoporosis as 'a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture'.[4] The WHO is currently developing algorithms to refine prediction of 5- and 10-year fracture risk in the individual patient. These algorithms will be based not only on BMD but also on a set of clinical risk factors for fractures that are independent of BMD, underscoring the necessity to combine BMD-independent fracture assessment with BMD for such predictions.[5]

The magnitude of the problem

Based on the WHO definition, it has been estimated that 30% of postmenopausal Caucasian women in the USA have osteoporosis at the hip, lumbar spine or mid-radius, and a further 54% have osteopenia at these sites.[6] Figure 2.1 shows the prevalence of osteoporosis and osteopenia amongst men and women in several age groups in the Rotterdam study, a large population-based cohort study of men and women aged 55 years and over in the Netherlands.[7]

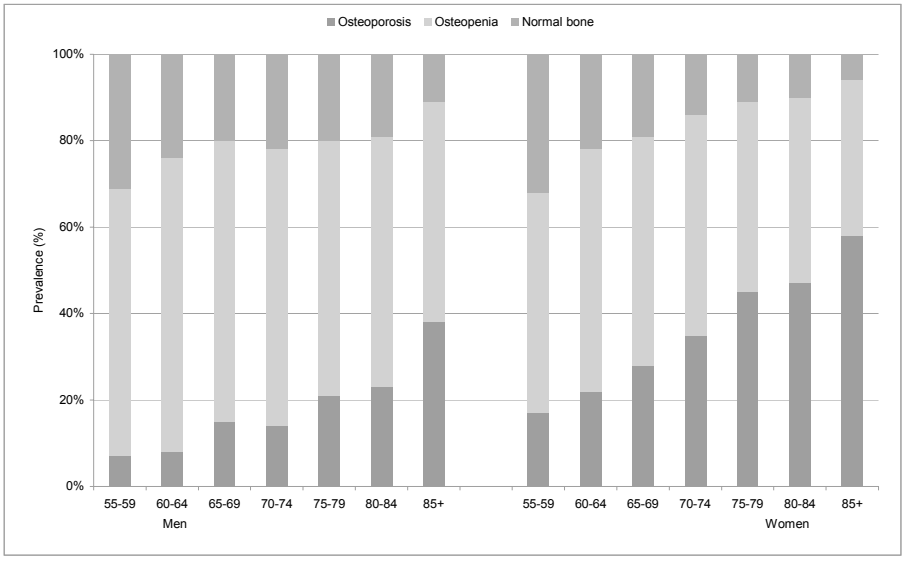

Figure 2.1 Prevalence of osteoporosis in men and women (the Rotterdam Study, 2004).

However, as mentioned before, low BMD alone is not the only determinant for an increased fracture risk. In the Rotterdam study the majority of fractures occurred in subjects who had a BMD T-score in the osteopenic range.[7] In the Study of Osteoporotic Fractures (SOF-study), a multicenter, observational study of 10000 older women, 74% of women of 65 years and over with a fracture did not fulfil the criteria of osteoporosis.[8] Eighty-two percent of women with a fracture of the distal forearm, hip or spine in the Nordic Research on Ageing (NORA) study also had no osteoporosis.[9]

Fragility fractures are an important public health issue because of the related morbidity and mortality. In white populations, about 50% of women and 20% of men older than 50 years will have a fragility fracture in their remaining lifetime.[6,10] Of the postmenopausal women with recurrent fractures, one out of four with a vertebral fracture will have another fracture within one year.[11] Women with a vertebral fracture have a fivefold risk for an other vertebral

fracture and a twofold risk for a hip fracture. About 6% of women and 11% of men die during hospital admission because of a hip fracture.[12]
Worldwide, elderly people represent the fastest growing age-group, and the yearly number of fractures is therefore likely to rise substantially with continued ageing of the population. Thus even if age-adjusted incidence rates for hip fractures remain stable, the estimated number of hip fractures worldwide will rise from 1.7 million in 1990 to 6.3 million in 2050.[13]
Fragility fractures also impose a major economic burden on health-care systems worldwide. The combined annual costs of all osteoporotic fractures have been estimated to be $20 billion in the USA, about $30 billion in the European Union[1] and € 210 million in the Netherlands.[14]

Clinical fractures

Most of the clinical fractures are due to a fall. As the risk to fall increases with ageing, this is another reason that the incidence of fractures increases with age. For vertebral fractures, however, falls play a less important role. The majority of vertebral fractures occur during routine daily activities such as lifting or changing position, though for many even no triggering activity or event can be identified.[15] When these fractures come to clinical attention, back pain is the most frequent presenting symptom. These fractures may also present with a range of other symptoms, including height loss, sleep disturbance, anxiety, depression, loss of self esteem, fear of falling, poor appetite and reduced quality of life.[16,17]

Morphometric vertebral fractures

Comparison of the incidence of clinically ascertained fractures with the estimated incidence derived from a population survey in the community indicates that only about one third of women with a vertebral fracture come to clinical attention because of lack of typical signs and symptoms of an acute fracture.[15,18] Radiographic survey of the spine is therefore required to document its prevalence and incidence. But even then fractures may be missed, as qualitative assessment of fractures from plain radiographs is often overlooked[19] and subject to observer disagreement. For this reason morphometric and semi-quantitative visual techniques have been developed and are now widely used in clinical and epidemiological studies.[20,21] Since there is as yet no consensus concerning the optimal criteria to determine whether or not a vertebral deformity is indeed a fracture, the prevalence and incidence of vertebral fractures is still ambiguous and heterogeneous between studies.
Data from the European Vertebral Osteoporosis Study (EVOS) indicate that 12% of men and women aged 50-80 years have evidence of a radiographic vertebral fracture.[22] Prevalence of these fractures increases with age in both

men and women. At younger age more fractures can be found in men than in women, probably as a result of trauma sustained during previous occupational or recreational activity.[23] The majority of morphometric vertebral fractures of the spine are found in the mid-thoracic area (T7-8) and the thoraco-lumbar junction (T12-L1).[24]

There are only a few population-based incidence data on vertebral fractures. Subjects in EVOS were followed prospectively and the incidence of a morphometrically defined vertebral fracture was 10.7/1000 person years in women and 5.7/1000 person years in men.[25] A similar incidence has been reported in the Rotterdam study.[26]

Recognition of all vertebral fractures is an important contributor to identifying patients at risk for further fractures, as the presence of both clinical and morphometric vertebral fractures are strong predictors of fracture risk, independent of BMD.[27]

Pathophysiology of fractures

From a mechanical perspective, fractures represent a structural failure of the bone, whereby the forces applied to the bone exceed its load-bearing capacity (Figure 2.1).[28] The forces applied to the bone will depend on the specific activity, and will vary with the rate and direction of the applied loads. The load bearing capacity of a bone (also referred as 'whole bone strength') depends on the amount of bone (i.e. mass, size), the spatial distribution of the bone mass (i.e. shape and microarchitecture), and the intrinsic properties of the materials that comprise the bone.[28] Thus, properties at the cellular, matrix, micro- and macroarchitectural levels may all impact the mechanical properties of bone.[29]

Bone must be stiff, able to resist deformation, so loading is possible. If bone is not sufficiently stiff – too flexible for the loads imposed on it – it will deform beyond its peak strain and crack. Bone must also be flexible, able to deform to allow energy absorption during impact loading. If bone is not sufficiently flexible – too brittle – the energy imposed on it will be released by cracking because it cannot deform 'enough' to absorb it when loaded. Bone must also be light to allow movement.[30] These seemingly contradictory properties, stiffness yet flexibility, and lightness yet strength, are determined by bone's material composition and how this material is fashioned into a three dimensional structure.[3]

A change in the material or structural components of bone, or the inability of bone modelling and remodelling to adapt these material and structural properties to the prevailing loads results in bone fragility (Figure 2.2).

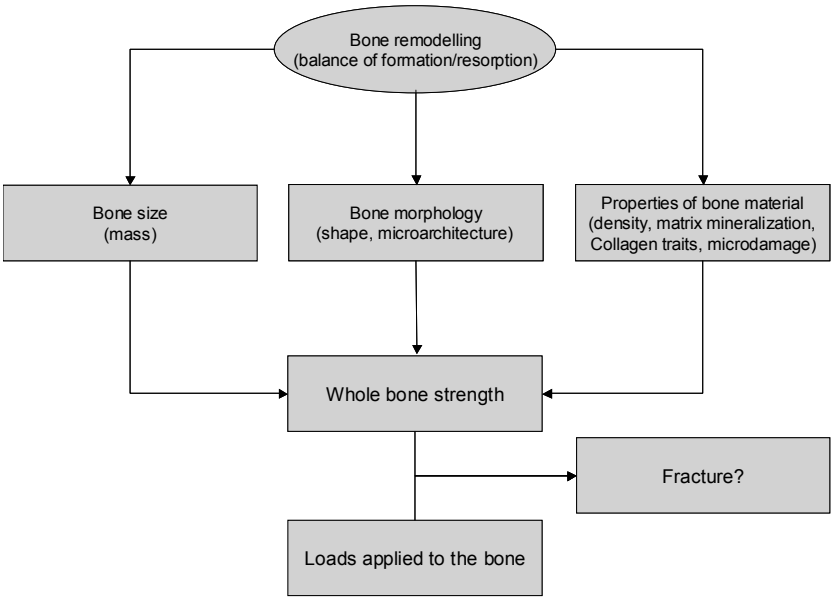

Figure 2.2 Etiology of age-related fractures and determinants of whole bone strength.

Although BMD remains currently the best available non-invasive assessment of bone mass in routine clinical practice, many other skeletal characteristics also contribute to bone strength. The recognition of these other determinants (often referred to as 'bone quality') is becoming more important, and their incorporation into algorithms of fracture detection remains the subject of continuing translational research.[31]

The bone mass of an individual in middle age is a result of the peak bone mass accrued during intrauterine life, childhood, and puberty, as well as the subsequent rate of bone loss. Bone loss takes place as a result of estrogen deficiency in postmenopausal women, as well as through estrogen-independent age-related mechanisms and is furthermore influenced by other factors, such as diseases and medications, and than referred to as secondary osteoporosis.

At the cellular level, bone loss occurs because of an imbalance between the activity of osteoclasts and osteoblasts. During life, the skeleton is continuously remodelled in an orderly sequence of bone resorption followed by bone formation – referred to as coupling. If the processes of resorption and formation are not matched, there is a remodelling imbalance. This imbalance can be magnified by a rise in the rate of initiation of new bone remodelling cycles (activation frequency).[31]

Bone remodelling

Understanding of the cellular basis of remodelling has advanced rapidly in recent years. The receptor activator of NFκB (RANK), its ligand (RANKL), and the decoy receptor Osteoprotegerin (OPG) are now known to be key regulators of osteoclastic bone resorption *in vitro* and *in vivo*.[32] The bone remodelling is initiated on a bone surface usually covered by a very thin layer of unmineralized matrix and lining cells. These cells may respond to stimuli (local and systemic cytokines, hormones), which initiate the remodelling. The differentiation of osteoclasts is stimulated and they start to restore bone. The stimulation of osteoclast activity requires an interaction with the osteoblastic cells. RANK ligand (RANKL) is expressed and secreted by osteoblast precursor cells and binds RANK expressed by osteoclasts, thus promoting the differentiation and activity of the osteoclasts. Osteoblasts secrete OPG which binds to RANKL and inhibits the RANK-RANKL interaction and thus acts as a physiological regulator of bone turnover.[3] (Figure 2.3)

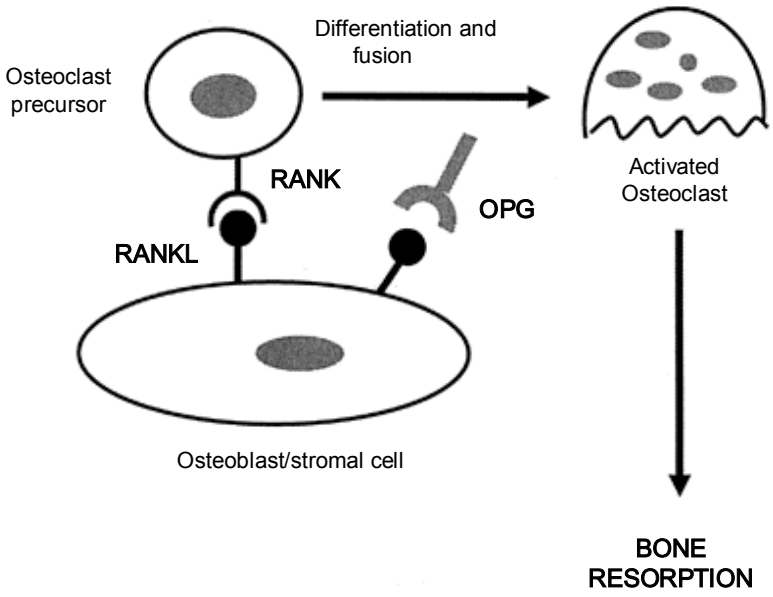

Figure 2.3 A schematic overview of the RANKL/RANK/OPG system.[33]

Osteoblasts and osteoclasts form the bone multicellular unit that reconstructs bone in distinct locations. Its purpose in adulthood is to maintain bone strength and to be available for adequate calcium homeostasis. In bone, damage due to fatigue develops during repeated loading, but only bone has the mechanism to

detect the location and magnitude of the damage, remove it, replace it with new bone, and then reconstruct the material composition, microarchitecture, and macroarchitecture.[30] The positive balance in the bone multicellular unit (net bone formation) during growth and the negative balance (net bone loss) during ageing are small. For these reasons, the rate of gain in bone during growth and loss during ageing is driven more by a high remodelling rate than by the magnitude of the positive or negative balance in the bone multicellular unit. Rapid remodelling is associated with an increased risk of fracture for several reasons. First, more densely mineralized bone is removed and replaced with younger, less densely mineralized bone, reducing material stiffness.[34] As a result, bone may become too flexible, bend excessively, and crack under usual loading conditions. Second, excavated resorption sites remain temporarily unfilled, creating stress concentrators that predispose bone to microdamage. Third, increased remodelling impairs isomerization and maturation of collagen, which increases the fragility of bone, probably by altering the cross linking between adjacent collagen fibrils.[35]

Bone remodelling is also influenced in the context of the calcium homeostasis. Calcium and vitamin D deficiency result in secondary hyperparathyroidism that increases bone remodelling and in variable degrees of mineralization defects, that contribute to bone deformities and fractures, such as in rachitis and osteomalacia.[36]

Recently, important novel genes and pathways for osteoblast differentiation and function have been discovered. In particular the identification of the role of the low-density lipoprotein receptor–related protein 5 (LRP5) gene in the regulation of bone mass is a landmark discovery. LRP5 is a modulator of osteoblast function and hence bone formation. It is a co-receptor for a series of osteoblast stimulating proteins operating through the Wnt signalling pathway. LRP5 is expressed on the osteoblast membrane between two other receptors, Frizzled and Kremen. Frizzled and LRP5 bind to Wnt, thereby activating bone formation.[31]

Last but not least, the central role of the osteocyte, the most frequent bone cell type, has been described in the context of signalling towards the osteoblast according to mechanical load on the skeleton, yet another pathway to influence bone remodelling. Recent discoveries have revealed the complex interaction between osteocytes with involvement of prostaglandins, sclerostin and Dickkopf.[31,37]

Assessment of fracture risk

Since 1994, the benchmark for the diagnosis of osteoporosis is the assessment of BMD. However, as mentioned before, low BMD alone is not the only determinant of fracture risk.[7] Although it is well established that the risk of

future fracture rises with the decline of BMD, it is nowadays evident that assessment of fracture risk should encompass all aspects of risk and that intervention should not be guided exclusively by results of bone mineral density measurements.[38]

Clinical risk factors

The WHO analyzed all international cohort studies in which information of clinical risk factors and bone mineral density are available and incident fractures have been ascertained.[38] On the basis of this information, several risk factors independent of bone mineral density have been identified. These include history of fracture, glucocorticoid use, family history of fracture, cigarette smoking, excessive alcohol consumption, rheumatoid arthritis and low body weight.

For the Dutch Guidelines on Osteoporosis, a clinical fracture risk assessment score is developed using the most important risk factors (Relative Risk of at least two compared to the general population risk).[12] Based on the risk score presented in Table 2.2, the individual absolute 10-year fracture risk can be calculated. When the risk score is 0, the absolute fracture risk in that part of the general population is on average half of that in the total population. With one risk factor present, fracture risk is doubled etc.

Table 2.2 Selected risk factors with the estimated associated relative fracture risk (Dutch Guidelines on Osteoporosis, 2002).

Risk factor	Fracture risk	Risk score points
Fracture after age 50 years	X 2	1
Prevalent vertebral fracture	X 4	2
Low body weight (<60 kg)	X 2	1
Severe immobility	X 2	1
Corticosteroid use (≥7.5 mg prednisolone daily)	X 2	1

Age

De Laet and co-workers clearly demonstrated that age and BMD are the two strongest independent risk factors for future fractures, both vertebral and non-vertebral and in both men and women.[39] The incidence of hip fractures increases both with decreasing BMD and with increasing age, and these two factors add independently to fracture risk in men and women equally. In addition, age can be regarded as a surrogate marker for various other risk factors for fractures, such as changes in bone remodelling and bone quality, increased tendency of falling, deficient calcium homeostasis and concurrent polymorbidity.

Methods to determine BMD

Dual-energy X-ray absorptiometry (DXA) is the most frequently used method for BMD measurement and is therefore considered the standard for the diagnosis of osteoporosis, the prediction of fractures and the follow-up of patients. Other methods to assess BMD are Quantitative Computed Tomography (QCT), Single-Energy Absorptiometry (SXA) and Quantitative Ultrasound (QUS). Although QCT is probably the best technique to assess bone mineral density separately in the trabecular and cortical bone compartment, it is not widely used because of lack of data on the predictive value for future fracture risk, high cost, limited availability, and, relative to DXA, a higher radiation dose needed for measurements.[40]

DXA

Bone density measurements with DXA are effective for predicting fractures in clinical practice and are stated to provide a gradient of risk that is as good or even better than other commonly used risk stratification measures such as blood pressure for stroke and serum cholesterol for cardiovascular disease.[41] The lumbar spine is the most optimal method to study changes in BMD by bone loss after menopause or increase in BMD by treatment, as the cell/bone ratio is highest in trabecular bone compartments.[42] Several studies have, however, revealed that with increasing age measurement of the spine is increasingly unreliable to document BMD, due to degenerative changes due to osteophytes and extra-osseous calcifications.[43] The hip represents both trabecular (trochanter) and cortical bone (femoral neck) and in a recent study hip measurements were found to be superior to the spine in overall osteoporotic fracture prediction.[44] This study showed that the commonly used rule of thumb that fracture rates double for each unit change in T-score clearly oversimplifies a more complex situation. The T-score in the hip had a much higher predictive value for fracture rates than the spine T-score. E.g. a women with spine T-score of -4.0 would be predicted to have only 2.8 times the risk of fracture of an otherwise identical woman with spine T-score of 0.0, whereas a femoral neck T-score of -4.0 would result in over a 10-fold relative fracture risk. Therefore the hip may be preferred as the primary site for diagnosis and fracture risk assessment as proposed by others.[38,45]

On the other hand, as mentioned earlier, a proportion of fractures occurs in patients with osteopenia rather than osteoporosis or even in patients with normal BMD.[7,8] This is partly due to the fact that BMD measurements by DXA reflect some of the components of bone strength, including bone mass, the degree of mineralization, and to some extent bone size. However, BMD measurements by DXA do not reflect other components of bone strength, including the three-dimensional distribution of bone mass, trabecular and

cortical microarchitecture, and the intrinsic properties of the bone matrix. To quantify these determinants high resolution CT-techniques are necessary. The first data of this technique indicate that indeed microarchitectural changes can be detected in the absence of osteoporosis.[46] The applicability and value of this technique over DXA in predicting fracture risk in daily practice is, however, not documented yet.

QUS

QUS measurements have been proposed as an alternative to BMD assessment with DXA.[47] Numerous ultrasound parameters used to characterize bone have been proposed, including broadband ultrasound attenuation (BUA) and speed of sound (SOS). In theory, QUS has the ability to provide additional information about bone structure, trabecular orientation and microarchitecture that is independent of bone mass and bone mineral density.[47,48] Moreover, QUS instruments have advantages compared with DXA: they are radiation-free, portable, and inexpensive.[49]

A number of cross-sectional studies have examined the relationship between QUS and fracture. These revealed a lower, an equal, as well as a higher prediction value than that obtained with DXA. In the Osteoporosis and Ultrasound Study (OPUS), the performance of five QUS devices was compared with DXA for discrimination of women with and without osteoporotic vertebral fractures. The calcaneus QUS appeared to be as good as axial DXA in discriminating women with vertebral fracture.[50]

The large prospective longitudinal EPIDOS and SOF studies investigated the efficacy of calcaneus QUS to predict fracture risk. The results of these studies are close to those obtained in cross-sectional studies. In the EPIDOS study, 5662 women (median age 80.4 years) were followed for 2 years. The risk of hip fractures increased for each SD decrease with BUA by a factor of 2 (1.6-2.4) and of 1.7 (1.4-2.1) by SOS. These results are similar to the predictive value of BMD after DXA, and remained significant after adjustment for BMD. The combination of QUS and BMD appeared not superior to the use of one of them alone.[51] The SOF study showed that each SD reduction of QUS increases the risk of hip (RR 2; CI 1.5-2.7) and vertebral (RR1.3; CI 1.3-1.5) fractures.[52]

Methods to determine bone turnover

Biochemical markers

Several biochemical markers of bone turnover have been developed. These provide non-invasive and fairly inexpensive methods to assess rates of bone formation (osteocalcin, bone alkaline phosphatase, peptides of type I procollagen) and resorption (deoxypiridinoline and its free and peptide-bound

forms such as carboxy-terminal cross-linked telopeptide of type 1 collagen) in vivo. However, the precise positioning of these biochemical markers in the clinical approach to osteoporosis management has not been established. The quality of these measurements has been improved with the introduction of automated immunoassay analysers.[53] Age, gender, ethnicity, menopausal status, disease status, recent fractures, immobility, certain pharmacological treatments and circadian variability were shown to influence the levels of bone markers.[54 55]

Bone turnover markers are mentioned to be of value to study the pathogenesis of osteoporosis, predict the risk of future fracture (independently of bone loss), and predict and monitor the response to therapy. Prospective studies have indeed shown an association between osteoporotic fractures and indices of bone turnover independent of bone mineral density in women during the menopause and in elderly women.[56] In elderly women with values of resorption markers exceeding the reference range for premenopausal women, fracture risk was shown to be increased about two-fold after adjustment for bone mineral density. These findings suggest that a combined approach using bone mineral density, clinical risk factors and markers of bone turnover may improve fracture prediction.[57]

Methods to determine fractures

Long bone fractures can easily be diagnosed with radiological images made after an appropriate trauma and typical clinical picture. This is unfortunately not the situation for a substantial number of vertebral fractures. The statement “there is no gold standard for the diagnosis or definition of a vertebral fracture” is repeated throughout the literature and illustrates the difficulties experienced in making a diagnosis of vertebral fracture.[58,59] Because a vertebral fracture is often unsuspected clinically, the diagnosis of vertebral fracture relies upon accurate interpretation of radiological images. Unfortunately, however, vertebral fractures are often missed in daily practice. In a large population of osteoporotic women recruited in a therapeutic trial, vertebral fractures were not adequately reported in the local radiology report in about 30% of patients.[60] The underdiagnosis of vertebral fractures was also evaluated in 934 hospitalized women who had a lateral chest radiograph. One hundred and thirty-two women (14%) were found to have moderate and severe vertebral fractures (Grades 2 and 3 according to Genant (Figure 2.4)), but only 50% of those were reported in the X-ray report and 23% in the medical report and thus treated.[19]

Vertebral fractures can be assessed by various methodologies. Radiologists, in routine clinical practice, usually visually analyze radiographs of the thoracolumbar spine in the lateral projection to identify vertebral fractures

(=visual, qualitative technique). While diagnosing the vertebral fracture in question, the interpreter also considers the potential differential diagnoses of this deformity. Advantages of this technique are detection of anatomic variants, detection of non-osteoporotic deformities and detection of technical features causing false positives. Disadvantages are inter- and intra-reader variability and therefore specific training and expertise is necessary.

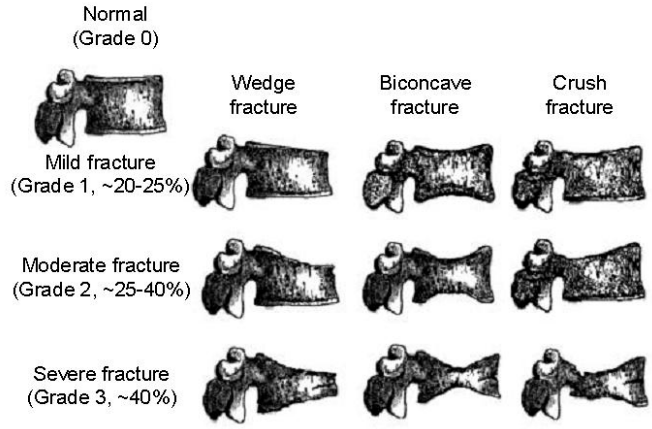

Figure 2.4 Semiquantitative technique of Genant.[63]

To provide in a more objective parameter, measurements of vertebral dimensions are developed and called quantitative technique or vertebral morphometry. Melton developed definitions of vertebral fractures utilizing percentage reductions in ratios of anterior, middle or posterior heights of vertebral bodies compared with normal values for that particular vertebral body.[18] Eastell modified this method, defining fractures on the basis of standard deviation reductions instead of fixed percentages.[61] More recently, McCloskey proposed a number of modifications to the Eastell/Melton standard criteria including the use of predicted posterior heights and the addition of more complex criteria.[62] Disadvantages of these methodologies are that the sensitivity and specificity are very much dependent on thresholds that define the prevalent and incident deformity and that there are no corrections for anatomical anomalies or other pathologies causing a deformity-like appearance.

In between these two techniques standardized visual assessment has been developed, also called semi-quantitative technique. One of these approaches is the method of Genant (Figure 2.4), in which the approximate degree of height reduction determines the assignment of grades to each vertebra; normal

(grade 0), mildly deformed (grade 1; approximately 20-25% reduction in anterior, middle and/or posterior height and 10-20% reduction of the projected vertebral area; moderately deformed (grade 2; approximately 25-40% reduction in heights and 20-40% reduction of the projected vertebral area) and severely deformed (grade 3; approximately 40% or greater reduction in heights).[63]

There are, however, also limitations of this semiquantitative grading scheme that may also apply to other standardized approaches. For example, from morphometric data on normal subjects we know that vertebrae in the midthoracic spine and in the thoracolumbar junction are slightly more wedged than in other regions of the spine. The consequence is that normal variations may be misinterpreted as mild vertebral deformities.[64] This may falsely increase prevalence values for vertebral fractures from visual readings in the specific regions.[65] The same applies to a lesser extent to the lumbar spine, where some degree of biconcavity is frequently seen. However, mild fractures detected with this method are also associated with a lower bone density than normal, and they also predict future vertebral fractures, although to a lesser extent than moderate or severe fractures do.[66]

Besides the discussion mentioned above about the different methodologies to define a vertebral fracture, there is also no gold standard for interpretation of radiographic images. Traditionally vertebral deformities have been identified on conventional lateral radiographs of the thoracolumbar spine (morphometric radiography or MRX). However, an alternative method of acquiring the lateral images of the spine has been developed, which utilizes DXA machines, commonly referred to as Morphometric X-ray absorptiometry (MXA) or Instant Vertebral Assessment (IVA). This technique has several advantages when compared with conventional radiography. These include a significant lower radiation dose to the patient, acquisition of a single image of the whole spine, fracture assessment can take place at the same time as bone densitometry, straightforward supine patient positioning and plan-parallel projection minimalising projection deformities.[67] However, image quality is less than that of the high-resolution conventional radiograph. Previous studies revealed nevertheless that this technique enables an accurate and precise measurement of vertebral dimensions, despite its moderate image quality.[67,68] This moderate image definition is, however, a significant drawback in assessing the upper thoracic region and in distinguishing fracture from other anatomical variants. There is good agreement between this technique and MRX in identifying fractures when strict criteria for fracture definition are used.[69]

Causes of osteoporosis; primary versus secondary forms

In the majority of patients osteoporosis is a result of bone loss due to the menopause and/or ageing. These situations are called primary osteoporosis.

Osteoporosis may, however, also be a consequence of certain diseases or medications and is then called secondary osteoporosis. Individuals with secondary osteoporosis experience bone loss that cannot be explained by the menopause or ageing only. The differential diagnosis for conditions and medications that contribute to secondary osteoporosis is extensive[36] (Table 2.3). Secondary osteoporosis is common in men and in premenopausal women with osteoporosis and in men and women with a recent clinical fracture.[70,71] In addition, as many as one third of women with postmenopausal osteoporosis have identifiable secondary causes that contribute to bone loss.[72] Secondary causes of osteoporosis in men account for 50-80% of cases of bone loss leading to fracture in this population.[72]

Table 2.3 Main conditions and medications that cause or are risk factors for secondary osteoporosis.

Disorders	Medications
Vitamin D deficiency	Heparin
Primary and secondary hypogonadism	Anticonvulsants
Inflammatory diseases (e.g. inflammatory bowel disease, rheumatoid arthritis, sarcoidosis)	Cyclosporine A
Gastrectomy	Glucocorticoids
Anorexia Nervosa	Lithium
Malabsorption e.g. Celiac disease	Methotrexate
Hyperparathyroidism	
Cushing syndrome	
Organ transplantation	
Hyperthyroidism	
Epilepsy	
Etcetera	

Glucocorticoid-induced osteoporosis

Glucocorticoid (GC) induced osteoporosis is the most common form of osteoporosis caused by medication. GC treatment leads to rapid bone loss and impairment of bone quality. GCs adversely affect bone remodelling by both reducing bone formation and increasing resorption. GCs have been shown to decrease osteoblastogenesis and osteoblast lifespan, and induce osteocyte apoptosis. GCs effects on bone resorption most likely result from accelerated osteoclast maturation and activity induced by reductions in gonadal and adrenal hormones and a negative calcium balance due to reduced gastrointestinal absorption of calcium in combination with an increase in urinary excretion.[73,74] The end result of these changes in bone metabolism induced by GCs is an increased fracture risk in patients exposed to these agents. Although the estimates of fracture risk on GCs varies, it may be substantial. Van Staa and colleagues reported in a meta-analysis an increase of vertebral fracture

rate up to fourfold after 3-6 months of therapy with a low dose of GCs (from an equivalent of prednisone of ≥2.5 mg daily).[75]

Osteoporosis in inflammatory diseases

It is well known that chronic inflammatory diseases affect bone physiology by the production of cytokines.[76-78] Inflammation has been shown to drive osteoclast differentiation and function by activating the RANK/RANKL (see Figure 2.3) pathway. Inflammatory cytokines (including TNF-α) and growth factors are shown to promote osteoclastogenesis with subsequent osteoclast-mediated bone loss. This growing interest in the interaction between inflammation and bone has resulted in the emerging field of osteoimmunology.[79]

Osteoporosis in inflammatory bowel disease

Decreased bone mineral density (BMD) and increased bone turnover are frequent findings in inflammatory bowel disease (IBD). On the basis of Z-scores, osteopenia can be found in 32 to 38 % of patients with Crohn's disease (CD) and in 23 to 25% of patients with ulcerative colitis (UC). An even higher prevalence of decreased bone mass can be found when a T-score is used to express changes in BMD.[80]

Factors contributing to decreased BMD in IBD patients involve inflammatory cytokines, malabsorption due to disease activity or extensive intestinal resection, GC use, inability to achieve peak bone mass when the disease starts in childhood, malnutrition, immobilization, low body mass index, smoking and hypogonadism induced by the chronic inflammatory condition.

Osteoporosis in sarcoidosis

Sarcoidosis is an inflammatory T-cell driven disease and as a result a decreased bone mineral density can be expected in this patient group. Besides this, prolonged treatment with GCs and decreased physical activity may also negatively affect bone. A limited number of studies on BMD measurements in untreated sarcoidosis are published. All these studies are of small size and revealed predominantly an unchanged BMD with only mild trabecular bone loss in longstanding sarcoidosis.[81-83]

Osteoporosis in thyrotoxicosis

The effects of thyroid hormone on bone metabolism are complex. Overt hyperthyroidism is associated with an increased risk of osteoporosis and the pathophysiology of it is multifactorial. This includes shortening of the bone remodelling cycle and acceleration of bone turnover.[84] Thyroid hormone indirectly promotes osteoclast formation and activation by inducing the

expression of cytokines, prostaglandins and the receptor activator of NFκB ligand (RANKL).[85]
A new development has been the discovery of functional thyrotropin (TSH) receptors in bone because of the implication that effects that traditionally have been attributed to high thyroid hormone levels may be in effect related to low TSH levels.[86] TSH inhibits RANKL and upregulates OPG thereby inhibiting bone loss. In subclinical hyperthyroidism TSH levels are characteristically low, resulting in an absence of this block and this can result in bone loss.
Bone loss is a uniform feature of overt hyperthyroidism. The extent of the reduction in bone density in most studies of hyperthyroid patients ranges from 10 to 20%.[87,88] A history of overt hyperthyroidism is a risk factor for hip fracture later in life,[8,89] and is one of the causes of excess late mortality in previously hyperthyroid patients.[90] It is therefore reasonable to assume that in some hyperthyroid patients bone density does not return to normal after antithyroid treatment. Symptomatic bone disease is not a prominent feature of subclinical hyperthyroidism. However, mild (subclinical) hyperthyroidism in subjects with multinodular goiter was associated with decreased forearm bone density, while in postmenopausal women with hyperthyroidism who were treated with methimazole a higher bone density of the distal forearm was found compared to untreated women.[91,92] In addition the risk of osteoporotic fractures may be increased.[93]

Prevention of fractures

Since most fractures occur as a result of falls, attention to reducing the risk of falls seems important. Targeted or broad spectrum fall prevention strategies have been shown to reduce the risk of falls, but none has shown anti-fracture effect. The use of hip protectors reduces the impact of falls on hip fractures in high risk individuals if worn at the time of a fall,[94] but low compliance remains the cause of lack of effect in the daily clinical setting.[95]
The drugs used to treat osteoporosis and to decrease fracture risk act on bone by manipulating bone turnover in quite different ways. Antiresorptive agents decrease bone resorption and bone formation, anabolic agents stimulate bone turnover (bone formation more than resorption) and strontium ranelate uncouples bone formation (increase) from bone resorption (slight decrease). With this classification, antiresorptive treatments include calcium, vitamin D, hormone replacement therapy, bisphosphonates, selective estrogen-receptor modulators (SERMs), and calcitonin.[31,42] The first clearly anabolic therapy that stimulates bone formation is recombinant parathyroid hormone (rhPTH).[96] Strontium ranelate has stimulated bone formation and inhibits bone resorption in animal models, but the exact anabolic mechanisms on bone formation in humans are under investigation.[97]

Whom to treat?

All clinical guidelines on postmenopausal osteoporosis recommend a case-finding strategy to identify patients at risk for fractures.[98] Patients are identified by the presence of well-defined clinical risk factors followed by measurements of BMD by DXA. Those with prevalent vertebral fractures or a BMD T-score less than -2.5 should receive treatment, although higher intervention thresholds have been proposed in the presence of clinical risk factors, such as prevalent non-spine fractures and use of glucocorticoids.

Treatment options

Many treatments are documented to reduce the risk of fractures in postmenopausal women with osteoporosis, including bisphosphonates (alendronate, risedronate, ibandronate, zoledronate), SERMs (raloxifene), strontium ranelate and rhPTH. However, the anti-fracture profile differs between these drugs in terms of spectrum of fractures prevented, speed of action in prevention of fractures, duration of the trials, safety, frequency of drug intake and compliance.

Management of secondary osteoporosis

Dual-energy X-ray absorptiometry is indicated in the initial workup of secondary causes of osteoporosis.[99] The presence of secondary causes of bone loss may further increase the risk of fracture independently of BMD and may necessitate earlier pharmacologic intervention. Management of bone loss in inflammatory diseases at this time should focus around reduction in inflammation and thus on treating the underlying disease.[36] Treatment with anti-tumor necrosis factor alpha (TNF-α) agents has been shown to reduce progression of juxta-articular bone loss in both rheumatoid arthritis and ankylosing spondylitis.[100,101]
Treatments directed at preventing the changes in bone metabolism induced by GCs are effective, and some have been shown to reduce fracture risk. The critical therapies include maintaining adequate calcium and vitamin D stores, prevention of falls by strengthening muscles associated with balance and ambulation, and bisphosphonates which have been shown to reduce fracture risk by 40-90%.[102,103] For the prevention and treatment of glucocorticoid induced osteoporosis, data are more compelling for bisphosphonates than for any other agent.[104]

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