Vertebral Fracture Initiative

Part I

Overview of osteoporosis:
Epidemiology and clinical management

Authored by:

Pawel Szulc[1], Mary L Bouxsein[2]

1. INSERM 831 Research Unit, University of Lyon, Hôpital Edouard Herriot, Lyon, France

2. Department of Orthopaedic Surgery, Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Reviewed by:

Juliet E. Compston
Department of Medicine, Addenbrooke's Hospital, Cambridge University, UK

Topics covered

I. Definition of Osteoprosis

In 1993, osteoporosis was defined as a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". A more recent definition from the NIH Consensus Development Panel on Osteoporosis defines osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Clinically, bone strength is estimated by non-invasive assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Numerous epidemiologic studies confirm that low BMD is among the strongest risk factors for fracture. As endorsed by the World Health Organization (WHO), the clinical diagnosis of osteoporosis is based on BMD measurements and the presence of fractures (1). For these diagnostic criteria, BMD is transformed into a T-score, which reflects the number of standard deviations (SD) above or below the mean in healthy young adults. The thresholds for each bone category are shown in the table below.

Table 1. WHO criteria for clinical diagnosis of osteoporosis

BMD T-score	Diagnosis
T-score $\geq$ -1	Normal
-1 > T-score > -2.5	Low bone mass
T-score $\leq$ -2.5	Osteoporosis
T-score $\leq$ -2.5 with existing fracture	Severe osteoporosis

II. Epidemiology and financial burden of osteoporosis

With advancing age, BMD decreases and prevalence of osteoporosis increases. In the United States, Europe and Japan, osteoporosis affects about 75 million people (2). Using the WHO criteria, 30% of postmenopausal Caucasian women have osteoporosis at the hip, lumbar spine or distal forearm (3). This is comparable with the risk of fracture for a 50 year old woman at one of these three sites. By the age of 80 years, 70% of women are osteoporotic at the hip, lumbar spine or distal forearm (3); in 2002, there were 8 million osteoporotic women and 2 million osteoporotic men in the US alone (4). The prevalence of osteoporosis, assessed using the reference values from the young population, varies by region. In Sweden 6.3 % of men and 21.2 % of women aged 50 to 80 were classified as osteoporotic (5),

whereas among individuals aged 80 to 84 years, 16.6 % of men and 47.2 % of women were osteoporotic.

Osteoporosis causes about 9 million fractures annually worldwide, of which more than 4.5 million occur in the Americas and Europe. The estimated lifetime risk for a wrist, hip or vertebral fracture is about 30 to 40% in developed countries, close to that for coronary heart disease. Hence, at the age of 50, a Caucasian woman's estimated lifetime risk of sustaining an osteoporotic fracture is 46-53% (6-7). In comparison, the estimated lifetime fracture risk for Caucasian men is 13 to 21%. The estimated lifetime risk of hip fracture in 50-year old Caucasians ranges from 17% to 23% in women, and from 6% and 11% in men. The risk of clinical vertebral fracture is slightly lower at age 50, with a lifetime risk of 15% in women and 8% in men (6). The lifetime risk of incident radiographic vertebral fractures in women is much higher ~27% and similar in men, 11% (8).

The risk of sustaining an osteoporotic fracture increases exponentially with age due to the decrease in BMD and the appearance of other age-related factors, e.g. increasing incidence of falls (**Figure 1**). Therefore, increasing life expectancy results in an increasing number of osteoporotic fractures. Moreover, age-adjusted incidence of fragility fractures have increased over the last three decades of the 20th century (9-10), partly, we believe because of a more sedentary lifestyle.

Of interest, the trend for increased age-adjusted incidence of fragility fractures has changed over the last 10 years. Although the age-specific incidence of osteoporotic fractures (mainly hip fractures) continues to increase in some countries (11-12), in other countries, it has leveled off or even slightly decreased (13-15). Several factors may contribute to this phenomenon. As life expectancy increases, at a given age an individual may be healthier. Higher prevalence of obesity and lower tobacco smoking habits improve the maintenance of bone mass (16-17) and greater use of anti-osteoporotic treatment may also decrease the number of osteoporotic fractures.

This recent reduction in age-adjusted incidence of fractures has only been observed in Western societies, and the impact of these positive trends on the number of the fragility fractures worldwide is limited. Thus, the greatest increase in the number of osteoporotic fractures (mainly hip fractures) can be expected in Middle East, Asia, and Latin America, where the life expectancy is predicted to increase the most in the coming decades. It is estimated that, in these regions, the total number of hip fractures will increase more than

fivefold between 1990 and 2050 (16) **(Figure 2)**. Men sustain 20 to 30% of all osteoporotic fractures and this proportion is expected to increase. Indeed, it is estimated that in 2025, the number of hip fractures occurring worldwide in men will be similar to that observed in 1990 in women (16). While men may also fall victim to other general trends which influence the fracture risk (increasing life expectancy, sedentary lifestyle), osteoporosis in older men continues to be underestimated, understudied, and insufficiently diagnosed and treated. Consequently, societal burden of osteoporosis in older men continues to increase.

Osteoporotic fractures are a major public health problem worldwide because of the associated morbidity, mortality and costs. The financial burden of osteoporotic fractures includes direct costs (hospital acute care, in-hospital rehabilitation, outpatient services, long term nursing care) and indirect costs (morbidity, loss of working days). Some costs are difficult to quantify, e.g. deterioration of quality of life, and time spent by the family on the care of the patient. Treatment of co-morbid conditions after a fracture constitutes 75% of the overall healthcare cost of osteoporotic fractures (19). Non-spine non-hip osteoporotic fractures are also responsible for a substantial proportion of the global health and economic burden of osteoporosis, mainly in people aged 50 to 65 years, when these fractures are 10 to 20 more frequent than hip fractures (20-21). Non-spine-non-hip fractures lead to hospitalization, disability, deterioration of life quality and loss of working days. In summary, osteoporosis is a serious public health problem and its social importance will increase further with the projected increase in the number of osteoporotic fractures and their financial and human costs.

Importantly, the financial cost of osteoporotic fractures is high and is increasing rapidly. In the USA, the estimated direct cost of osteoporosis is 19 billion in the US in 2005 and expected to increase by 50% by 2025 (22). Every year in the USA, 3.5 million hospital bed days are attributed to osteoporotic fractures and over 60,000 nursing home admissions are attributed to hip fractures. Trends are similar in Europe, where the estimated cost of osteoporotic fractures was 36 billion euro in 2000 and is expected to double to 77 billion euro by 2050 (23-24).

In conclusion, in all countries, osteoporotic fractures are expensive and their costs are projected to increase on a per-fracture basis and also because the total number of fractures is projected to rise. However, the net financial burden depends on the healthcare level and economic status of the country. Thus, the higher number of fragility fractures due to the

increasing life expectancy in developing countries may constitute a serious challenge for their economies during the coming decades.

III.   Pathogenesis of osteoporosis and risk factors for fracture

Age-specific changes in BMD

Bone mass and BMD increase rapidly during childhood and adolescence, key times for longitudinal and radial skeletal growth. During this time, increase in areal BMD (g/cm^2) is largely related to the increase of bone size. In boys, longitudinal growth lasts for a longer period of time than in girls, both before and during puberty. Therefore, men are taller than women. Radial growth in boys also lasts for a longer period of time than in girls. Therefore, men have wider bones than women even after adjustment for height and length of body segments (25). As areal BMD depends partly on bone size, men have higher BMD when measured by dual-energy X-ray absorptiometry (DXA). After growth stops, consolidation is the final phase of the formation of peak BMD (26). Subsequently, two processes determine changes in BMD: periosteal apposition and bone loss which involves trabecular bone and the endosteal surface of the cortical bone (27). In young adults, these processes are in equilibrium and areal BMD is stable. When bone loss outweighs periosteal bone gain, BMD begins to decrease.

Age-related bone loss is greater in women than in men. During the first years after the menopause, there is rapid bone loss, largely in the trabecular compartment, that leads to trabecular perforation followed by loss of entire trabeculae (28). When the trabeculae disappear, the metabolically active surface available for bone resorption decreases and trabecular bone loss slows down. Cortical bone loss also accelerates with age and consists of cortical thinning and increasing cortical porosity. By the age of 80, the amount of trabecular and cortical bone lost is around 40 % from the premenopausal peak BMD (27).

In men, slow bone loss starts soon after attainment of peak BMD then accelerates exponentially after the age of 70 (29-30). In men, trabecular bone loss consists mainly of trabecular thinning which compromises bone strength less than the loss of entire trabeculae (28). The mechanism of cortical bone loss is similar in both sexes but of smaller magnitude in men (31). The lifetime bone loss in both compartments in men is about 20 to 25 %. Thus, in men, peak BMD is higher and bones are larger, whereas aging-related bone loss is of smaller

magnitude and structurally less detrimental to bone strength in comparison with women. Therefore, the age-specific incidence of osteoporotic fractures is lower in men than in women.

Hormonal disturbances

The hormonal changes occurring at menopause are a major factor leading to osteoporosis in women. An abrupt reduction in ovarian function results in a rapid decrease in 17β-estradiol secretion which leads to an increased secretion of cytokines that activate osteoclasts, including RANKL, interleukin-1β, interleukin-6 and tumor necrosis factor α. The resulting increase in bone resorption leads to bone loss and microarchitectural deterioration, as described above.

In men, gonadal function decreases slowly. Even in older men, the average concentration of total testosterone is only 20 % lower than in young men and, in many elderly men, the total testosterone level remains in the normal range (32). By contrast, concentrations of bioavailable and free testosterone are 50-60 % lower than those found in young men. However, the main sex steroid regulating bone turnover in older men is 17β-estradiol, especially its bioavailable fraction (33). Men with the lowest bioavailable 17β-estradiol levels have lower BMD, higher levels of biochemical bone turnover markers (BTM), accelerated bone loss, a higher prevalence of vertebral fractures and higher incidence of hip fracture (33-35).

Secondary hyperparathyroidism due to vitamin D and calcium deficit also contributes to bone loss in elderly men and women. Intestinal calcium absorption decreases with age. Decreased synthesis of endogenous vitamin D results from aging of the skin and from lower sunlight exposure. Decreased synthesis of $1\alpha,25$-dihydroxycholecalciferol [$1\alpha,25(OH)_2D$], the active form of vitamin D, results from the age-related reduction in the activity of renal enzyme 1α –hydroxylase. Decrease in $1\alpha,25(OH)_2D$ production contributes to the decrease in intestinal calcium absorption and circulating calcium levels. Consequently, the secretion of parathyroid hormone (PTH) increases and PTH stimulates bone resorption, mainly in the cortical bone.

Other risk factors for osteoporosis and for osteoporotic fractures

Many studies highlight the role of hereditary factors in the pathogenesis of osteoporosis. Epidemiological studies show a significant correlation of BMD in twins, the correlation being stronger in monozygotic than dizygotic twins. Furthermore, women whose mothers sustained a hip fracture have a lower BMD and a higher risk of fragility fracture

compared to women whose mothers did not suffer a hip fracture. Indeed, twin and family studies suggest that up to 80% of the variability in peak bone mass is attributable to genetic factors (36). Whereas a number of gene variants have been implicated in low BMD and increased fracture risk, genes responsible for the specific heritable component of osteoporosis have not been conclusively identified (37).

Lifestyle factors that increase the risk of low BMD and fractures include alcohol abuse, smoking, low calcium intake, and lack of physical activity. These factors are inter-related: smokers tend to drink more alcohol, often have a poorer diet and take less physical activity. They also tend to be thinner. Lifestyle factors also interact with other factors; for example, components of tobacco smoke influence enzymes involved in the metabolism of steroid hormones.

Some diseases also increase the risk of osteoporosis, including hyperthyroidism, Cushing's disease, haemochromatosis, primary biliary cirrhosis, hypogonadism, multiple myeloma, chronic obstructive pulmonary disease, beta-thalassaemia, and diseases of the digestive tract impairing intestinal absorption such as Crohn's disease, coeliac disease and chronic pancreatitis. Some drugs increase the risk of osteoporosis, e.g. glucocorticoids (especially long-term oral use), thyroid hormone excess (mainly suppressive treatment after thyroid cancer), anti-androgen treatment (gonadotrophin releasing hormone agonists, surgical castration), aromatase inhibitors, thiazolidinediones, loop diuretics, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs) and some drugs used in the treatment of AIDS (mainly tenofovir, protease inhibitors).

Risk factors for fractures

Epidemiologic studies have identified several factors that increase an individual's risk of fracture. While a thorough review is beyond the scope of this document, several key risk factors are highlighted. Among the strongest risk factors for fracture are low BMD, advanced age, female sex, Caucasian ancestry, and previous history of fracture. Specifically, the risk of fractures is markedly increased (two- to four-fold) in subjects with prevalent fragility fractures, regardless of age and BMD. In addition, factors that increase the likelihood of falling are associated with fractures. Hence the risk of fracture is higher in patients with condition that increase the risk of falls (hemiplegia, frailty, lower limb dysfunction, Parkinson's disease, cardiovascular disorders leading to orthostatic hypotension) and among patients treated with neuroleptics, antidepressants and antihypertensive drugs. As noted in the

following text, several diseases and medications can increase the risk of fractures. Interested readers are encouraged to read one of several reviews on the risk factors for fractures (38-41).

IV. Osteoporotic fractures – clinical manifestation of osteoporosis

Vertebral fractures

Vertebral fracture is the most common osteoporotic fracture. They may occur in the absence of trauma or after only minimal trauma, such as bending, lifting or turning. In individuals aged over 50 years, the prevalence of vertebral fracture is similar in men and women, largely due to increased presence of traumatic fractures in men that were incurred during their youth (42). In a study performed in different European countries where all radiographs were analyzed in one reference centre, the prevalence of vertebral fractures varied from 10-24% according to the diagnostic criteria (43-44). Prospective epidemiological studies show that the incidence of new vertebral fractures in elderly men is half that occurring in women of the same age (45-47). Annually, one 65 year old woman among a sample of 100 and one man among a sample of 200 will sustain a new vertebral fracture. The incidence of vertebral fractures increases dramatically with age (45, 48). For instance, the risk of sustaining a new vertebral fracture is about two times higher at 75 years of age than at 65 years of age.

Vertebral fractures have a major personal and societal impact in terms of disutility and financial costs (49). The clinical symptoms of vertebral fractures are back pain, limitation of spine mobility, loss of height and disability (50-52). They can be associated with difficulty in bending, rising, dressing, climbing stairs, as well as reduced pace of walking, reduced independence or even the need to use a walking aid (43, 50, 53-57). Back pain and disability as well as difficulties in performing activities of daily living are observed mainly in patients with fractures in lower thoracic and lumbar spine, whereas fractures in the mid-thoracic spine can result in a mild reduction of pulmonary function (56, 58-59).

Vertebral fractures result in a deterioration of the health-related quality of life mainly through back pain, reduced physical capability, perceived poor general health and emotional status (e.g. fear of falling, lack of independence, purposeful limitation of activity and of social interactions) (60-61). Deterioration of quality of life is more pronounced in patients with several vertebral fractures (59). Incident vertebral fractures are associated with a marked deterioration in the quality of life and with an average bed rest ten times higher than in osteoporotic women without incident vertebral fracture (52, 56).

The risk of vertebral fractures increases significantly with decreasing BMD (61-63), and these fractures are an important clinical manifestation of osteoporosis. A vertebral fracture (assessed using a standard radiograph or Vertebral Fracture Assessment software) is an independent predictor of subsequent osteoporotic fractures, especially of the spine and hip (64-66) **(Figure 3).** After adjustment for age and BMD, a prevalent vertebral fracture is associated with a four- to five-fold increased risk of suffering a subsequent vertebral fracture (65, 67-68). The risk of a new vertebral fracture increases with both the number and the severity of prevalent vertebral fractures (69-71). A fifth of osteoporotic women with a recent vertebral fracture will sustain a new vertebral fracture within the next 12 months, highlighting the need for prompt diagnosis and rapid, effective treatment (72).

In addition, epidemiological studies report a higher mortality in patients with osteoporotic vertebral fractures, with age-adjusted mortality rates increasing with the number of vertebral fractures (73-76). For example, clinical vertebral fractures are associated with an 8-fold increase in age-adjusted mortality, which is similar to the increase in mortality seen following a hip fracture (73) **(Figure 4)**. The excess mortality in patients with vertebral fractures may, in part, be attributable to their poorer health status (77). The financial burden of vertebral osteoporosis and associated fractures is significant and, in the elderly, includes the costs of hospitalization and of subsequent rehabilitation (78-79). In the working population, medical costs associated with vertebral fractures are related to outpatient care and to the loss of working days.

However, despite their major personal and societal impact, vertebral fractures often do not come to clinical attention. This is thought to be for two main reasons. Firstly, about two thirds of vertebral fractures do not give clinical symptoms and may be only detected on a radiograph. Clinical symptoms of vertebral fractures are not specific and may be confused with osteoarthritis and other causes of back pain. Secondly, even on spine radiographs, vertebral fractures are often undiagnosed. In a large population of osteoporotic women recruited into a therapeutic trial, vertebral fractures were not adequately reported in at least 30% of patients (80) and this poor result was obtained in reference centers focused on osteoporosis. The rate of under-diagnosis may be even higher in general clinical practice. Vertebral fractures are not appropriately reported in the radiology and medical records (and, consequently, in healthcare insurer databases) (81). In elderly hospitalized patients who had a lateral chest radiograph, less than 50% of vertebral fractures identified later on X-rays were reported in the radiological reports and even fewer in the medical records (82-83).

Consequently, only about 40% of older women with vertebral fractures visible on X-ray are referred for DXA measurement of BMD and receive adequate anti-osteoporotic treatment (83-85) **(Figure 5)**. The figure is even lower (less than 20%) for men.

Thus, the clinical importance of vertebral fractures can be summarized as follows:

1. **Vertebral fractures are common in both women and men and their incidence increases with age.**

2. **Vertebral fractures increase the risk of new vertebral fracture four to five-fold and the risk of other fragility fractures two- to four-fold.**

3. **Vertebral fractures are associated with an increased mortality.**

4. **Vertebral fractures lead to chronic pain, kyphosis, height loss, disability, and reduced quality of life.**

5. **The presence of a low trauma vertebral fracture is a clear indication of the need for treatment for osteoporosis, independent of BMD and of other risk factors.**

Hip fractures

Hip fracture is one of the most disastrous consequences of osteoporosis. Its incidence increases exponentially with age in men and women (47, 86). The two main determinants of the risk of hip fracture are low BMD and increased risk of falls (63, 87-89). Many risk factors for hip fracture act through these two determinants. Low BMD is attributable to increasing age, low body mass index (BMI), weight loss after the age of 25 years, lack of physical activity, poor nutrition, tobacco smoking, chronic alcoholism, gastrectomy, certain diseases, and some medications (mainly glucocorticoids, loop diuretics and thyroid hormones) (90-91). The risk of hip fracture is also increased in people with prevalent fractures, mainly vertebral and distal radius fractures, regardless of BMD (92-93).

The risk of falls also increases with age, especially in the frail elderly with compromised neuromuscular function, poor physical performance, visual impairment, or insulin-treated diabetes (94-100). The impact of the fall depends on its direction (falls sideways on the hip are more likely to lead to fracture) and on the thickness of tissues surrounding the upper part of femur (96, 101-102). Aging is associated both with a decrease in BMD and with an increased risk of falls. Poor nutrition, vitamin D and calcium deficit as well as protein deficiency are common in the elderly and contribute to bone loss and to a loss

of fat and muscular tissue which results in a higher risk of falls and poor protective mechanisms.

Mortality is increased 15 to 25% in the year following hip fracture, with particularly high rates in men (73-75, 103-104). Hip fractures frequently result in a temporary or permanent loss of independence, institutionalization and permanent deterioration of quality of life (105-106). A substantial number of people with hip fracture experience a second hip fracture which is characterized by higher mortality than the first fracture (107). The cost of hip fracture is high and includes hospitalization, surgical treatment and rehabilitation as well as the costs of outpatient care, particularly institutionalization (105, 108).

Non-hip-non-spine fractures

Fracture of the distal radius is one of the most frequent osteoporotic fractures in women and one of the earliest manifestations of osteoporosis. Its incidence increases in the early postmenopausal years and then stabilises (86, 109). In men, the incidence of distal radius fractures increases with age only slightly and remains low throughout life (86). In elderly men, the incidence is four times lower compared with women of the same age (86, 110). In postmenopausal women, risk factors for this fracture are advancing age, an early menopause, low BMD, low BMI, falls (mainly falling forward on the hand), prevalent fragility fractures, height loss (often due to vertebral fractures), and a history of parental osteoporotic fractures(63, 96, 101, 110-113).

Fracture of the distal radius rarely requires hospitalization. However, it is associated with a temporary decrease in independence, deterioration in quality of life and, in working people, loss of working days (20). Sudeck's atrophy is a common complication of fracture of the distal forearm. While this fracture is often considered a minor fracture, people who have sustained this fracture have a two to three times higher risk of other osteoporotic fractures, mainly of the hip, pelvis, vertebrae and humerus (92, 109, 114). Therefore, it should be regarded as the first signal of osteoporosis necessitating full diagnostic assessment (20).

Fracture of the proximal humerus is common in osteoporotic patients. After 50 years of age, its incidence increases with age in both men and women (86, 110, 115). However, at any given age, its incidence is two to three times higher in women compared with men (9, 86, 110). Similar to other fragility fractures, the two main risk factors for fracture of the proximal humerus are low BMD, mainly at the distal forearm, increased risk of falls and prevalent fragility fractures (63, 88, 90, 95, 112, 116). Proximal humerus fracture results in a temporary

loss of independence, deterioration in the quality of life, increased risk of hip fracture and increased mortality (74, 104). Other common sites for fragility fractures are the ribs, pelvis, clavicle, femur and tibia. These fractures are important for two principal reasons (20). Firstly, they may be the first manifestation of osteoporosis and associated increased bone fragility. Secondly, they may have important personal and societal consequences.

V.   Diagnostic procedures

Dual-energy X-ray absorptiometry (DXA)

Evaluation of BMD by DXA is based on measuring the differential tissue-dependent (bone vs soft tissues) absorption of energy from two photon beams of different energy obtained using an X-ray source (117). DXA is used to measure BMD at the lumbar spine, hip, distal forearm, calcaneum and whole body. It measures areal BMD, expressed in g/cm^2, which depends on the volumetric BMD (vBMD, expressed in g/cm^3) and on bone size. Thus, areal BMD does not distinguish if higher BMD relates to a higher amount of bone mineral or simply bigger bones. However, fracture risk is determined by the degree of bone mineralization and by bone size. Therefore, a greater areal BMD is significantly associated with a reduced risk of fracture, even after adjustment for confounding factors.

Stability, accuracy (trueness) and reproducibility (precision) are principal parameters of reliability of DXA measurements. Stability of the DXA device should be confirmed by daily measurement using a spine phantom. Accuracy is important for the screening of patients and for assessment of fracture risk. DXA is reliable in diagnosing osteoporosis and evaluating fracture risk. Although there is a normal biological variability of BMD at various skeletal sites, values of BMD at different sites of measurement are strongly correlated in an individual. Thus, measurement of BMD at two skeletal sites provides a good evaluation of the bone status and of the general fracture risk. However, the best predictor of the risk of fracture at a given site is BMD measured at this site (118). Hence hip fracture risk is best predicted by hip BMD, whereas vertebral fracture risk is best predicted by spine BMD.

Reproducibility is important mainly in the prospective evaluation of bone loss and of the effect of anti-osteoporotic treatment. As precision error (1-2 %) is high compared with the rate of bone loss or bone gain during anti-osteoporotic therapy, a minimum interval of two years between measurements is necessary for monitoring therapeutic efficacy. The accuracy and the reproducibility of the BMD measurement depends on two components: stability of the

DXA device on one hand and, on the other hand, correctness and consistency of the positioning of the patient.

The **lumbar spine** is a common site for assessment by bone densitometry. However, presence of osteoarthritis results in a false increase in BMD in the elderly, especially in men (119). The presence of scoliosis or of lumbar vertebral fractures may give rise to inaccurate measurement of the spine BMD. Correct identification of lumbar vertebrae L1 to L4 is necessary to provide a correct assessment of the spine BMD. Therefore, it is important that the scan window is sufficient to visualise the iliac bone and lowest ribs which are helpful as landmarks for the identification of vertebrae. Measurement of lateral BMD eliminates the posterior arch with its processes and has been suggested as a method to partially reduce the effect of osteoarthritis on BMD in the lumbar spine; however, its accuracy error is high. Moreover, in some patients (especially in the elderly), upper lumbar vertebrae are partly covered by the lowest ribs, whereas L4 may be partly covered by the iliac crests, which renders this measurement unreliable.

The **total hip and its components** are a reliable site of measurement especially in elderly subjects who have a high risk of hip fracture and in people with severe lumbar osteoarthritis, scoliosis or fracture (117, 120). The best sites are the femoral neck and total hip. Both predict fracture risk equally well. The total hip area is more suitable for monitoring treatment as it is a large area comprising cortical and trabecular bone. By contrast, BMD measurements in the trochanter and Ward's are not useful in clinical practice. Appropriate positioning (slight internal rotation of the lower limbs) is particularly important to obtain reliable data. It should be also stressed that different manufacturers use different definitions of the region of interest (ROI) of the femoral neck and of the lower border of the total hip area.

Several devices measure BMD of the **distal forearm**. The most distal enlarged part of the radius is composed mainly of trabecular bone whereas the cortical envelope is thin (except subchondral cortical bone). The most proximal ROI measured, called the one-third-distal radius, is composed of about 95% cortical bone. The intermediate ROI is composed mainly of cortical bone and the trabecular fraction depends on the segment of the radius measured by a given type of DXA device. Different devices for evaluating distal forearm BMD use different algorithms to define the limits of the ROIs and measure slightly different parts of bone. Therefore, results obtained using different devices should not be compared (121-122).

Quantitative computed tomography (QCT)

In quantitative computed tomography (QCT), the X-ray source and detector rotate in a synchronized fashion around the subject as X-rays are passed through the body. Mathematical algorithms are then used to reconstruct the attenuation data into 3D images. Use of a bone mineral (or hydroxyapatite) phantom allows calibration of the image data, providing a measurement of bone density that unlike DXA is independent of bone size and can be obtained separately in the trabecular and cortical bone compartments.

QCT-based bone measurements have been used to evaluate sex-, age-, and ethnic-related differences in vertebral and femoral geometry, thereby providing new insight into the development of skeletal fragility (123-126). Studies have demonstrated that whereas bone density declines with age in both sexes, bone loss is much greater, particularly in the trabecular compartment, in women than in men (123). Due to its ability to isolate a volume of trabecular bone for analysis, QCT has also afforded insights into the mechanisms of drug therapies that are not apparent with standard DXA measurements (127-129). In particular, increases in vertebral trabecular bone density following teriparatide treatment are two- to three-fold greater than changes in spine aBMD by DXA. There are numerous cross-sectional studies showing an association between QCT bone density and fracture risk, though no consensus on whether QCT performs better than DXA. There are few studies demonstrating the ability of QCT to predict fracture risk prospectively, though several large cohorts have recently included QCT measurements and are following subjects for fracture outcomes, so these data will likely be available soon.

Standard QCT techniques generate images with in-plane voxel sizes of approximately 300 to 500 μm and slice thickness of 1 to 3 mm, and are therefore not adequate to assess trabecular bone microarchitecture, as trabecular thickness ranges between approximately 100-200 μm and trabecular separation between approximately 300-500 μm. Recently, however, high-resolution imaging with multislice spiral CT (HRCT) scanners has been used to assess vertebral trabecular architecture, achieving images with an in-plane resolution of 156 to 187 μm and slice thickness of 300 to 500 μm (130). A preliminary, cross-sectional study indicated that HRCT provides superior discrimination of vertebral fracture patients compared to BMD (131). HRCT was recently used to monitor changes in vertebral trabecular architecture following one year of teriparatide therapy, thus providing information that was distinct from BMD measurements (132).

Overall, the advantages to QCT are that it can be employed on standard clinical scanners with relatively short imaging times, providing robust assessment of geometry and volumetric

bone density in trabecular and cortical compartments at sites most prone to fracture, although the radiation exposure is a concern for some subjects (133). Additional data are needed on the ability of QCT-based measures to predict fracture risk prospectively.

High resolution peripheral quantitative computed tomography (HR-pQCT)

Recently, a high-resolution, peripheral CT (HR-pQCT) system capable of achieving resolutions of up to 80 µm at tolerable radiation doses has been introduced for assessment of trabecular and cortical microarchitecture in the distal radius and distal tibia (134-139). This technique has excellent precision for both density (<2%) and microstructure (<4%) measurements (134). Longitudinal HR-pQCT measurements indicate that whereas substantial cortical bone loss begins in middle life in women, it does not commence significantly until after age 75 in men (136). In contrast, trabecular bone loss begins early in adulthood in both women and men, such that approximately 40% of total life-time trabecular bone loss occurs before age 50, as compared to less than 15% for cortical bone.

Although no prospective fracture trial results are currently available, several cross-sectional studies have reported that microarchitecture measurements at the distal radius by HR-pQCT discriminate postmenopausal women with a history of fragility fracture from those who have not suffered a fracture, partly independently of BMD (134, 137-138). There are no studies showing treatment-related changes bone architecture as assessed by HR-pQCT. Altogether, HR-pQCT technique is highly promising for assessment of trabecular and cortical architecture in vivo and has high precision. However, it requires specialized scanners, and measurements are limited to peripheral skeletal sites.

Quantitative ultrasonography

In quantitative ultrasonography (QUS), bone mass is assessed by two main parameters of ultrasound transmission: speed of sound (SOS) and broadband ultrasound attenuation (BUA) (140). QUS equipment evaluates bone integrity at the calcaneus, phalanges of the fingers, patella and tibia (140-141). The calcaneus should be very sensitive to disturbances of bone turnover because it contains 90 % trabecular bone which is metabolically very active. It has been claimed that QUS reflects not only bone quantity but also its trabecular microarchitecture and material properties of bone such as elasticity and stiffness. However, there are few experimental data to support this claim (142).

The degree of technical diversity of QUS devices is larger than in DXA. This increases the difficulties in comparing measurements between different QUS devices and may lead to misinterpretation of results (140). Correlation between QUS and BMD measured at different sites is modest (140). In epidemiological studies carried out in men and women, the predictive value of QUS for osteoporotic fractures is comparable to that of DXA or only slightly lower (143-145).

Despite several advantages (noninvasive, free of ionizing radiation, small inexpensive equipment which can be easily transported), QUS has not acquired a place in routine clinical practice. The long term stability of these devices is often poor. Values of QUS parameters measured *in vivo* depend on the temperature of the water bath and skin, positioning of the foot, the concentration and type of detergent and the soft tissue thickness. There are no QUS-derived diagnostic thresholds of osteoporosis. Furthermore, it is not clear whether QUS could be helpful for the assessment of bone loss and for initiating anti-osteoporotic treatment. QUS should not be used for monitoring of anti-osteoporotic treatment. Quality control procedures and standardization of the regions of interest require further improvement.

Magnetic resonance imaging (MRI)

Magnetic resonance (MR) imaging offers a non-ionizing method to assess bone microarchitecture (146-147). The most common MRI approach for bone quality assessment uses a strong magnetic field in combination with specialized sequences of radiofrequency pulses to generate 3D images of bone structure (146). Because free hydrogen in water generally provides the 'signal' in this type of MR imaging and since the water content of bone is minimal, there is generally little signal provided by bone in standard MR imaging. As a result, bone structure is assessed indirectly via measurements of the surrounding marrow and other soft tissues. Advances in the past decade have focused on image acquisition and analysis techniques to overcome inherent obstacles in MR imaging of bone (147).

High-resolution MR imaging of bone structure is generally performed at peripheral skeletal sites (e.g., distal radius, distal tibia, calcaneus) using clinical MR scanners combined with specially designed coils. Using this approach, in vivo resolutions of 150 - 300 μm in plane and a slice thickness of 300 - 500 μm have been achieved (148-149). With this resolution, it is not possible to produce accurate values for most features of trabecular architecture. Nonetheless, the "apparent" trabecular properties that are derived from these images correlate strongly with measurements of trabecular architecture obtained with higher resolution

techniques (150-151). Interestingly, a newly introduced MRI system can acquire image data with 0.160 x 0.160 x 0.160 cubic voxel size, but this system is presently limited to imaging the middle phalanx (152). Until recently, evaluation of trabecular bone morphology was limited to appendicular sites. However, innovative surface coils and pulse sequences show potential for MR-based assessments of trabecular structure in the proximal femur (153).

MR-derived trabecular microarchitecture measurements have been shown to reflect age- and disease-specific differences (154-155), and to differentiate patients with hip and vertebral fractures from control subjects, with the best performance provided by combinations of structural parameters and BMD (156-161). There are no studies demonstrating prospective fracture risk prediction and limited data on treatment-related changes (162-163). Currently, MRI is only used in research studies and its application for the clinical management of osteoporosis is not yet established.

Biochemical markers of bone turnover

Measurement of biochemical bone turnover markers (BTM) is a noninvasive method to evaluate bone metabolism. There are two groups of BTM. Biochemical markers of bone formation include serum concentrations of proteins secreted by active osteoblasts: osteocalcin, bone specific alkaline phosphatase (BAP), procollagen type I N-propeptide and C-propeptide (164). Biochemical markers of bone resorption are mainly products of catabolism of resorbed type I collagen measured in serum and urine: C-terminal and N-terminal crosslinking telopeptides of type I collagen, deoxypyridinoline (crosslinking molecule) and certain amino acids such as hydroxyproline or galactosylhydroxylysine.

In the research setting, BTM are useful to study the mechanisms of physiological or pathological phenomena at the level of bone tissue. In particular, they enhance understanding of the effects of anti-osteoporotic medications on bone remodeling and the dynamics of changes in BMD. However, not all research applications of BTM can be transferred into clinical practice. For instance, whereas increased BTM levels are associated with faster bone loss in epidemiologic studies, BTM measurements cannot be used for the prediction of accelerated bone loss in individual patients (165), although BTM (BAP and bone resorption markers) may help to identify older women at high risk of fracture (165-166). BTM also have potential for monitoring osteoporosis therapy, as bisphosphonates lead to profound reductions in BTM whereas teriparatide leads to a profound increase, particularly in P1NP (165, 167). In addition, BTM may be used to improve the persistence of patients on bisphosphonates.

Specifically, informing the patient that he or she had a substantial decrease in the BTM level during anti-resorptive therapy has been shown to improve persistence with treatment, although persistence with treatment also decreased in patients who were informed that their BTM level did not decrease significantly (168-169). These latter patients need a more careful assessment of the lack of decrease of the BTM level despite the therapy, e.g. lack of adherence, or incident disease associated with faster bone turnover such as multiple myeloma. Overall, the results of BTM should be interpreted cautiously because of their substantial biological variability, which can be minimized by collecting samples under standardised conditions, with fasting morning samples being the most reliable.

VI.   Clinical assessment of osteoporosis

In addition to clinical risk factors, the principal tool in the assessment of osteoporosis and of the risk of fracture is BMD measured by DXA. Osteoporosis and osteopenia are diagnosed using the aforementioned cutoffs proposed by the WHO (Table 1). However, DXA and the WHO definition have some limitations. This definition was established for postmenopausal Caucasian women and its extrapolation to men and to women from other ethnic groups may be problematic. Furthermore, although BMD is strongly correlated between skeletal sites in the population, BMD has its own variability at each skeletal site. Thus, T-score varies in one person according to the skeletal site and, consequently, the prevalence of osteoporosis (percentage of the population diagnosed as osteoporotic) varies according to the skeletal site. From the practical point of view, BMD measurement of the hip is the most reliable as it avoids the artifacts associated with degenerative changes in the spine. According to the WHO guidelines, a T-score threshold of ≤ -2.5 is the clinical diagnosis for osteoporosis. This cutoff is justified by epidemiological studies and by clinical observations. However, the fracture risk increases progressively with decreasing BMD (gradient of risk) and these cutoffs are somewhat arbitrary. Average risk of fracture in osteopenic women is lower than in osteoporotic women (even if an individual risk for fracture in an osteopenic woman with several clinical risk factors may be higher than in an osteoporotic woman with no other risk factors). However, there are many more osteopenic than osteoporotic women and therefore, the majority of osteoporotic fractures occur in osteopenic, not osteoporotic, women. In fact, only 20 to 40% of individuals who suffer a fracture have a T-score <-2.5, and thus most individuals with a fracture have low to normal BMD as measured by DXA.

Various attempts have been made to improve the identification of subjects at high risk of fracture. Several clinical scores have been published which included simple clinical factors such as age, weight (or BMI), falls, previous fragility fractures. The WHO Fracture Risk Assessment Tool (FRAX®) is a new algorithm that uses clinical risk factors that are partially independent of BMD to improve fracture risk prediction in postmenopausal women and men aged 40 years or over (170). It has been calculated on the basis of data from several large long-term prospective cohort studies and is available online (http://www.shef.ac.uk/FRAX). The risk factors used in FRAX® include age, weight, height, previous fragility fracture, parental hip fracture, current smoking, regular intake of 3 or more units of alcohol daily, rheumatoid arthritis, oral glucocorticoids (current therapy or former exposure to glucocorticoids) as well as, alternatively, causes of secondary osteoporosis or femoral BMD. FRAX® calculates the 10-year probability of fracture and helps to make individualized therapeutic decisions. However, it does not replace clinical judgment. Firstly, to be clinically useful, the algorithm has to be based on simple dichotomized criteria (yes/no) and cannot take into account various degrees of severity of medical conditions, e.g. number, site and severity of previous fragility fractures, or dose and duration of tobacco smoking, alcohol intake and glucocorticoid treatment. Secondly, FRAX® does not include potential risk factors which are difficult to quantify (e.g. diseases increasing risk of fall and compromising protective reflexes,) or were not consistently assessed in previous studies (age at the menopause, BTM, presence of morphometruc vertebral fracture, rate of bone loss, bone geometry, bone microarchitecture) (171). Thirdly, spine BMD cannot be entered into FRAX®, and fracture probability may therefore be underestimated in individuals with a low spine, but normal hip BMD, Finally, FRAX® is not designed to evaluate fracture probability in individuals who have already received bone protective therpy.

Altogether, the clinical management of osteoporosis should include several components: assessment of clinical risk factors, BMD measurement, exclusion of other diseases and causes of low bone mass (e.g. myeloma, osteomalacia, intestinal absorption disorders), followed by assessment of the risk of fracture on the basis of BMD and other risk factors, and finally choice of the most appropriate form of treatment (172).

VII. Treatment of osteoporosis

Several effective medicines are approved for the prevention and treatment of osteoporosis. These agents have been demonstrated to reduce vertebral, and in some cases non-vertebral, fracture risk in women with osteoporosis. They can be broadly divided into two categories: anti-resorptive (or anti-catabolic) or anabolic agents. Anti-resorptive agents, which include estrogen, the selective estrogen receptor modulator raloxifene, bisphosphonates and the human monoclonal antibody to receptor activator of NFκB ligand (RANKL) reduce bone resorption (and subsequently bone formation), leading to an increase in BMD to varying degrees. In comparison, anabolic agents, which include full-length parathyroid hormone (PTH1-84) and teriparatide (PTH1-34) stimulate bone formation (and subsequently bone resorption), thereby increasing BMD. Strontium ranelate is another agent that reduces fracture risk. It has only weak effects on bone remodeling and probably improves bone strength mainly through effects on bone material properties.

In postmenopausal women with osteoporosis the primary outcome investigated in pivotal pharmaceutical trials is reduction of fracture. Risk reductions of between 30 and 70% have been demonstrated for vertebral fractures, around 15-20% for non-vertebral fractures and up to 40% for hip fracture (173-174). However, of the currently approved treatments only alendronate, risedronate, zoledronate and strontium ranelate have been shown to reduce vertebral, non-vertebral and hip fractures. In men and in glucocorticoid-treated populations regulatory approval has been obtained on the basis of bridging studies, in which similar BMD changes to those seen in postmenopausal women with osteoporosis, have been demonstrated.

Calcium and vitamin D

Available evidence does not support a role for calcium and vitamin D alone in prevention of osteoporotic fractures except in the institutionalized elderly population [175]. In the home-dwelling population, studies of native vitamin D have produced conflicting results which may be related to the dose of vitamin D and calcium supplementation. Vitamin D at the dose of 700 to 800 IU with 1000 to 2000 mg calcium daily significantly reduced the incidence of non-vertebral fractures by 23%, including a significant 26% decrease in the risk of hip fracture (176-177). In contrast, a lower dose of vitamin D (400 IU daily) did not reduce fracture risk (178). Higher doses of vitamin D that result in serum 25OHD >60 nmol/L may decrease the risk of falls (179).

Active metabolites of vitamin D (1α-hydroxycholecalciferol [1α(OH)D], 1α,25(OH)$_2$D) are used for the treatment of osteoporosis in certain countries. Two meta-analyses show that both forms of vitamin D significantly decrease the incidence of fragility fractures, at least in patients who were not treated with glucocorticoids (180-181). However, these results are partly based on studies of suboptimal methodological quality (181), thus, the evidence base for the anti-fracture efficacy of the active metabolites of vitamin D is weak.

It should be noted that placebo and treatment groups in all pharmaceutical trials received calcium and vitamin D. Therefore, the anti-fracture efficacy demonstrated by these agents was above and beyond what was provided by calcium and vitamin D alone. Furthermore, the efficacy of these drugs was only established in subjects who were calcium and vitamin D replete, an important concept to keep in mind when initiating therapy with one of these agents.

Hormone replacement therapy

Hormone replacement therapy (HRT) may consist of estrogens alone or in combination with progestin. HRT slows bone turnover and increases BMD at all skeletal sites in early and late postmenopausal women (182-183). The anti-fracture efficacy of HRT has been assessed in observational studies, case-control studies, meta-analyses and randomized clinical trials (Women's Health Initiative [WHI], Heart and Estrogen/progestin Replacement Study [HERS], Women's Interventional Study of long Duration Oestrogen after Menopause [WISDOM]). Overall, these analyses (except HERS) show that HRT decreases fragility fracture risk by 20 to 35 % (184-186). However, discontinuation of HRT results in acceleration of bone turnover, decrease in BMD and eventual loss of anti-fracture efficacy.

Despite this anti-fracture efficacy and a decrease in the risk for colon cancer, overall health risks generally outweigh benefits from HRT in older postmenopausal women with a higher incidence of cardiovascular events (unstable angina, thromboembolic stroke, venous thromboembolism including pulmonary embolism) and increased incidence of endometrial and breast cancer (184-187). HRT can also induce vaginal bleeding and breast tenderness. Finally, HRT may increase the risk of myocardial infarction, ovarian cancer as well as deterioration of global cognitive function.

More recent studies show that even low doses of HRT may protect bone by decreasing BTM levels and preventing bone loss (188-189). The anti-fracture efficacy of these regimens

has not been studied. Currently, HRT is regarded as an acceptable treatment for osteoporosis only after all other treatments have been considered and when all the risks and benefits are carefully explained to the patient. Women who decide to take HRT to relieve menopausal symptoms should use the lowest effective dose and for the shortest possible time (187).

Selective estrogen receptor modulators (SERM)

Selective estrogen receptor modulators (SERM) are synthetic molecules that have the ability to bind to estrogen receptors throughout the body and act as estrogen agonists or antagonists depending upon the target organ. The concept of SERM is based on the observation that tamoxifen, used as an anti-estrogen in the treatment of breast cancer, acts as an estrogen agonist on bone in postmenopausal women. Raloxifene (60 to 120 mg daily) slows down bone turnover (decrease in the BTM levels by 35%) and increases BMD by 2 to 3% at the lumbar spine and femoral neck (190-191). It reduces the incidence of vertebral fractures by 40 to 50% (192-194). No effect was observed on nonvertebral fractures, except a 22% decrease in the incidence of major osteoporotic fractures in women with prevalent vertebral fractures, mainly severe vertebral fractures (195-196).

Raloxifene markedly reduces the risk of invasive estrogen-receptor positive breast cancer (194, 197-198). In most studies, raloxifene did not influence the risk of cardiovascular (coronary) events (194, 199) and, in some groups, may even decrease the risk of myocardial infarction or unstable angina (200). It increases the risk of venous thromboembolism to the same extent as HRT and increases the risk of fatal stroke mainly in women with high risk of stroke at baseline (194, 201-203).

Another SERM, bazedoxifene (20 to 40 mg daily), decreases BTM levels to a similar extent as 60 mg raloxifene daily, increases BMD of the lumbar spine by 2 % and prevents bone loss at the total hip (204-205). It decreases the risk of vertebral fracture by 40%, similarly to raloxifene, and decreases by 40% the risk of nonvertebral fracture in women at higher risk of fracture (low femoral neck T-score and presence of vertebral fractures at baseline) (205). In postmenopausal osteoporotic women at high risk of fracture assessed by FRAX[®], bazedoxifene decreased the risk of morphometric vertebral fracture by 50% and the risk of all clinical fractures by 30% (206). In these studies, risk of cardiovascular events, cerebrovascular events, thromboembolism and of cancer was similar in the women treated

with bazedoxifene, raloxifene and placebo. Bazedoxifene is not yet approved for the prevention or treatment of osteoporosis.

Bisphosphonates

Bisphosphonates (BP) are potent inhibitors of bone resorption and inhibit the activity of osteoclasts. All approved bisphosphonates have been shown to reduce vertebral fracture risk and increase BMD, while some have also demonstrated reductions in non-vertebral and hip fracture risk. They are available as oral and IV formulations, with weekly, monthly and annual dosing schedules, depending on the specific agent. Bisphosphonates bind to bone mineral, and consequently have a long skeletal retention. Orally administered BPs have a poor intestinal absorption and can induce mild intestinal disturbances.

<u>Alendronate</u> decreases bone resorption and formation markers, increases BMD and reduces the incidence of fractures by 30 to 50 % in women with established osteoporosis (207). Anti-fracture efficacy has been shown both in women with prevalent vertebral fractures and in women with low BMD (T-score <-2) but without vertebral fractures (207-208). Meta-analyses carried out using data from several studies in postmenopausal and elderly osteoporotic women have shown that alendronate decreases the risk of hip fracture by about 45 % (209). Bridging studies have shown that once-weekly alendronate at a dose of 70 mg is therapeutically equivalent to the reference daily regimen (similar increase in BMD, similar decrease in BTM levels) (210). In early postmenopausal women, a smaller dose of alendronate (5 mg) prevents bone loss (211). In osteoporotic men, alendronate increases BMD at the lumbar spine and hip and decreases the incidence of vertebral fractures (212). Alendronate also prevents bone loss in men receiving androgen deprivation therapy for prostate cancer (213) and is effective in the treatment of glucocorticoid-induced osteoporosis (214). Rare cases of esophagitis have been reported.

<u>Risedronate</u> decreases the incidence of new vertebral and peripheral fractures by the same extent as alendronate in women with low BMD and in women with prevalent vertebral fractures (215-216). In osteoporotic women 70 to 79 years of age, risedronate decreased the incidence of hip fracture by 40 % (217). Bridging studies have shown that alternative doses of risedronate (35 mg once a week, 75 mg on two consecutive days a month, 150 mg once a month) decrease BTM levels and increase BMD to a similar extent as the daily regimen (218-

220). In men with low BMD, risedronate decreased bone turnover and increased BMD (221). The efficacy of risedronate has also been shown in the prevention and treatment of glucocorticoid -induced osteoporosis (222).

In a post-hoc analysis carried out in data combined from four phase III studies, risedronate reduced the incidence of fractures within 6 months of treatment (223). Some (224), but not all (225), observational studies suggest that the anti-fracture efficacy of risedronate appears earlier than that of alendronate. However, these analyses are based on the retrospective analyses of the databases of the healthcare providers and no randomized head-to-head studies permitting direct comparisons were performed.

Ibandronate is commercially available as an oral daily regimen (2.5 mg/day), oral monthly regimen (150 mg once monthly) and intravenous form (3 mg i.v. every 3 months). In postmenopausal osteoporotic women, oral ibandronate administered daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months) induced a rapid, pronounced and persistent decrease in bone turnover, increased BMD and reduced the incidence of vertebral fractures by at least 50% (226-227). Oral ibandronate administered at a dose of 150 mg once monthly induced a greater decrease in BTM levels and a significantly greater increase in BMD than daily ibandronate (228). Once-monthly ibandronate (150 mg) also reduced the risk of vertebral fractures to a similar extent as weekly alendronate and risedronate (229). In postmenopausal osteoporotic women, intravenous ibandronate (2 mg every 2 months or 3 mg every 3 months) induced a similar decrease in BTM levels, a greater increase in BMD and a similar reduction in the incidence of clinical fractures in comparison with daily ibandronate (230). Meta-analyses of the results of all the existing studies showed that the annual cumulative exposure (ACE) to ibandronate higher than 10.8 mg was associated with a decrease in the incidence of the non-vertebral fractures by about 30 to 40 % (231-232). (Please note: calculation of ACE takes account of the intestinal absorption of a drug and corresponds to its quantity which is available to bone tissue.) In male cardiac transplant patients, ibandronate (2 mg *i.v.* every 3 months) decreased BTM levels, prevented bone loss and reduced the incidence of vertebral fractures (233).

Zoledronic acid administered intravenously to postmenopausal women with osteoporosis at a dose of 5 mg *once-yearly* induced a sustained decrease in bone turnover, a progressive increase in BMD and a significant decrease in the incidence of vertebral fractures by 70 % and in the incidence of non-vertebral fractures by 25 % (including a significant 40 % decrease in the incidence of hip fractures) (2341). In older men and women with recent low trauma hip

fracture (two weeks or later but less than 90 days after surgical repair) zoledronic acid increased BMD at the hip, decreased the incidence of clinical fractures (including a significant decrease in the incidence of hip fracture) and reduced the mortality rate by about 30 % (235-236). In men and women treated with oral glucocorticoids, zoledronic acid induced a greater decrease in the rate of bone turnover and a greater increase in BMD compared with risedronate (237). In men receiving androgen deprivation therapy for prostate cancer, zoledronate slowed bone turnover and prevented bone loss (238).

Possible side effects and limitations of bisphosphonates

Recently, several issues related to long-term use of BPs have been raised. An important and associated question is how long patients should be treated with BPs. BPs are potent suppressors of bone resorption and may lead to a phenomenon called "severely suppressed bone turnover" (239), particularly in patients on glucocorticoid therapy and/or concommitent anti-resorptive therapy, such as HRT. Such extreme inhibition of bone remodeling may theoretically lead to an accumulation of microdamage which might compromise bone strength and increase the risk of low trauma fracture or delay fracture healing (239-241). However, iliac crest biopsies from women on long-term bisphosphoante do not show increased microdamage (242), and clinical trials of bisphophonates did not show evidence of altered healing.

To avoid potential side effects, many clinicians consider it apropriate to re-evalute the patients fracture risk after 5 years of treatment, and then consider whether to stop or continue the treatment. There is limited evidence to support this key clinical decision. In the FLEX trial, withdrawal of alendronate after 5 years of treatment was followed by a mild decrease in BMD (at some, but not all sites) and a mild increase in BTM levels (243-244). In another study, fracture incidence after BP discontinuation increased in women who took BPs for 2 years with a suboptimal adherence (245). By contrast, after discontinuation of long term treatment with alendronate in the FLEX study, fracture incidence remained reduced for 5 years, except for a slightly higher risk of clinical vertebral fractures in comparison with women who took alendronate continuously (243). However, there was no placebo group in this study, so it is difficult to draw firm conclusions. Thus, there are no evidence-based guidelines how long osteoporotic patients should take BPs. However, on the basis of the

available clinical and pre-clinical data, it can be inferred that, in the vast majority of patients, stopping therapy is more likely to do harm than continuing therapy (246).

Osteonecrosis of the jaw (ONJ) is observed in patients with various malignancies who are treated for a long period of time with high doses of BPs (247-248). By contrast, cases of ONJ in osteoporotic patients are extremely rare – no case was found in more than 3000 patients participating in the clinical trials with zoledronate and alendronate (234-235, 243) and no causal link between ONJ and BP therapy in these patients has been convincingly demonstrated. Precipitating factors for ONJ, which occurs in people who have never received BP therapy, include dental surgery, ill-fitted dental prosthesis and aggravating factors (heavy smoking, infection) (249-251). Clinical data do not support the use of BTM (e.g. serum CTX-I concentration) as predictors of the risk of ONJ in the bisphosphonate-treated patients (252).

Recent case reports have suggested a higher occurrence of atypical femoral shaft fractures (subtrochanteric or proximal diaphyseal fracture) in a select group of women and men treated long-term with alendronate, particularly in those receiving glucocorticoids and/or another anti-resorptive medication such as estrogen (253-258). It is not clear if these fractures are related to long-term alendronate treatment or rather are a form of fragility fracture in osteoporotic patients. These fractures are generally thought to be low trauma fractures occurring in patients who have taken alendronate for several years (usually > 5). Prior to their fracture, these patients often, but not always, had experienced persistent pain in the thigh that was, aggravated during standing and resistant to analgesics. Individuals with these types of fractures appear to have modest cortical thickening of the femur diaphysis, and bone scintigraphy shows increased uptake of the radioisotope in the subtrochanteric area at the site of the cortical thickening which can be bilateral, and which is consistent with a stress fracture. These two factors are important for physicians treating patients with these agents. Hence, a pain in the thigh not related to trauma and aggravated by standing needs further investigation when it is reported by a patient treated with alendronate. Secondly, it is advisable to discontinue alendronate in patients with normal BMD values on long-term glucocorticoid treatment. Additional studies are needed to determine the mechansims underlying these fractures and the characteristics of the few patients that may be at increased risk for this injury.

Treatment with BPs has been associated with a higher risk of atrial fibrillation in some (234, 259-260), but not all (261-262), studies. The association between use of BPs and risk of atrial arrhythmia and its clinical significance remains to be elucidated. Women treated for

osteoporosis may have a higher cardiovascular risk before the beginning of the BP treatment than non-osteoporotic women. During treatment with zoledronate, electrolyte imbalance does not seem to precipitate the atrial arrhythmia, because episodes of atrial fibrillation did not cluster in time after infusions, when serum electrolytes are most affected (234).

Salmon calcitonin

Salmon calcitonin is commercially available as an injectable formulation and as a nasal spray. This 32-amino-acid peptide secreted by the C-cells of the thyroid inhibits activity of osteoclasts, slows bone resorption, but induces only a mild increase in BMD (263). Nasal salmon calcitonin decreased the incidence of vertebral fractures by 33% in older osteoporotic women, most of whom had prevalent vertebral fractures (264). The anti-fracture effect was observed after at least 3 years of treatment and only for the dose of 200 I.U. daily, but not for those of 100 and 400 I.U. daily. There is no evidence for efficacy of nasal salmon calcitonin on non-vertebral fractures. In men with idiopathic osteoporosis, nasal salmon calcitonin reduces bone turnover and increases lumbar spine BMD (265). Of interest, salmon calcitonin appears to reduce the pain associated with acute vertebral fractures (266). Salmon calcitonin is safe apart from very rare allergic reactions. However, due to its limited anti-fracture efficacy relative to other available agents, nasal salmon calcitonin is not considered a first-line therapy.

Antibody to Rank Ligand: Denosumab

Denosumab prevents the binding of receptor activator of nuclear factor-κB ligand (RANKL) to receptor activator of nuclear factor-κB (RANK) on the cells of the osteoclastic lineage. RANKL binds to RANK and stimulates osteoclast differentiation, activation and survival. Denosumab is a fully human monoclonal antibody that binds to RANKL with high affinity and specificity. It blocks the interaction of RANKL with RANK and inhibits bone resorption. In postmenopausal women with low BMD, denosumab administered *s.c.* 60 mg every 6 months increased BMD by 1 to 7% according to the skeletal site (267). It inhibits bone resorption strongly and rapidly, e.g. serum CTX-I decreases by more than 80% one week after denosumab injection. In postmenopausal osteoporotic women, denosumab decreased the risk of vertebral fracture by 70% (including a 60% decrease in the incidence of

multiple vertebral fractures) and the risk of non-spine fractures by 20% (including a 40% decrease in the incidence of hip fracture) (268). Also in older men receiving androgen-deprivation therapy for prostate cancer, denosumab slowed bone turnover, increased BMD by 4 to 7% as well as decreased the incidence of vertebral fractures by 60% and the incidence of multiple fractures by 70% (269).

Anabolic agents: PTH and teriparatide

Recombinant 1-34 fragment of human parathyroid hormone [rhPTH(1-34), teriparatide] and recombinant human intact parathyroid hormone [PTH(1-84)] are effective stimulators of bone formation. They stimulate bone remodeling at the bone remodeling unit and bone modeling on quiescent bone surfaces. They induce a prompt increase in bone formation followed by a slower increase in bone resorption. As they strongly increase BMD in the trabecular compartment, the greatest increase in BMD is observed at the lumbar spine.

In the cortical sites, they slightly decrease areal BMD measured by DXA (one-third distal radius) and volumetric BMD measured by QCT (femoral neck, total hip). By contrast, they increase cortical bone volume at the radius and femoral neck (270-271). In osteoporotic women with prevalent vertebral fractures, rhPTH(1-34) decreases the incidence of new vertebral fractures by 65 % and of non-vertebral fractures by 53 % (272). In postmenopausal women with low BMD, PTH(1-84) decreased the incidence of vertebral fractures (but not of non-vertebral fractures) by about 60 % (273). The fracture incidence remained significantly decreased for at least 30 months after discontinuation of teriparatide treatment (274). However, these data should be interpreted cautiously, because during the follow-up after the discontinuation of teriparatide, patients and investigators were unblinded to the treatment and additional treatment for osteoporosis was allowed. The best candidates for anabolic treatment are patients with preexisting osteoporotic fractures, patients with very low BMD and those with unsatisfactory response to ant-resorptive therapy (275).

Teriparatide and PTH(1-84) increase BMD and reduce the risk of fracture mainly by stimulating bone formation, thus, by a different mechanism from that of BPs. Therefore, a logical question was whether joint use of two groups of drugs would provide therapeutic advantage. This point is important because anabolic treatment necessitates daily subcutaneous injection. However, after one year of combination therapy of PTH(1-84) and alendronate, no

synergy was observed and alendronate even attenuated the effect of PTH(1-84) on BMD (127). In osteoporotic women taking alendronate for at least 1 year, continued alendronate plus rhPTH(1-34) s.c. daily for 3 month cycles alternating with 3-month periods without rhPTH(1-34) induced similar increase in BMD and in BTM levels to continuous rhPTH(1-34) (276). Treatment with oral alendronate (10 mg daily for 1 year) after 1-year treatment with PTH(1-84) allowed a further increase in BMD at the lumbar spine and the hip (271). These studies were made in small groups without assessment of the anti-fracture efficacy. However, they suggest that the therapeutic effect PTH may be obtained by less frequent administration of PTH with alendronate.

Strontium ranelate

Strontium ranelate (2 g daily) slightly inhibits bone resorption, slightly stimulates bone formation and progressively dose-dependently increases BMD (277-278). It decreases the incidence of vertebral fractures by about 40 % (277). During long-term treatment (4 years), strontium ranelate decreased vertebral fracture incidence by 33% (279). Strontium also decreases the incidence of vertebral fractures by 35% in younger postmenopausal women (aged 65 or less) and by 32% in the elderly women aged 80 and over (280-281). Strontium ranelate decreases the incidence of non-vertebral fractures by about 15% and even more (31%) in the oldest women (281-283). Post-hoc analyses demonstrated that strontium ranelate decreases the incidence of hip fracture by approximately 40% in high risk elderly women with severe osteoporosis (282-283).

VIII. Clinical management of vertebral fractures

Short-term clinical management of vertebral fractures is dominated by treatment of symptoms, which may include back pain, depression and respiratory symptoms due to decreased pulmonary function. Treatment of back pain comprises bed rest, pharmacological treatment (analgesics or narcotics), physical therapy, bracing, local steroid injections and vertebral augmentation (vertebroplasty, kyphoplasty) (284).

Pharmacological treatment of back pain

Pharmacological treatment of back pain is often needed in subjects with vertebral fractures. While opioids can be necessary, pain related to inflammation within the periosteum and adjacent soft tissues in patients with recent fractures may respond to nonsteroidal anti-inflammatory medications. In addition, opioids may pose risk in elderly patients, particularly altered mentation, somnolence, interference with balance and risk of falls.

Purely analgesic treatment may be supported by other drugs such as antidepressants, anticonvulsants or alpha-2-agonists. Among the antidepressants, tricyclics, selective serotonin-reuptake inhibitors and monoamine oxidase inhibitors are used most often and at lower dose than that required for their antidepressant effect. Anticonvulsants suppress spontaneous neuronal firing rates via their action on ion channels and/or neurotransmitters. As various anticonvulsants act on various receptors, response to one does not predict a response to another one in this class. Central alpha-2-agonist, tizanidine, helps to control pain; however, cardiovascular side effects must be monitored. Two principles have to be respected for these medications. The initial dose should be small and gradually increased. Then, after the treatment, a medication should be tapered off in order to avoid withdrawal phenomena.

Physical therapy

Physical therapy has two principal aims in treating painful vertebral fractures. Firstly, painful vertebral fractures decreases the number of activities of daily living which a patient can perform. Thus, education in activities of daily living in ways to avoid the pain is essential to preserve (or restore) everyday functioning and quality of life of these patients. Secondly, therapeutic exercises can reduce pain and strengthen muscles. In the initial phase (soon after the fracture), mild physical exercises reduce compressive loads on the spine and, consequently, reduce acute pain, improve posture and body mechanics. Later on, physical therapy should be focused on strengthening of spinal extensors, abdominal, gluteal and hip muscles and on dynamic proprioceptive training (especially in patients with scoliosis). This treatment reduces chronic backache, helps to support spinal structures, decreases the fear of fall and improves the quality of life (285). Obviously, all physical therapy should avoid activities with positions that provoke pain.

Bracing

The aim of bracing is to reduce pain, to facilitate immobilization, to enhance healing, to ensure correct posture and to provide support in patients with significant muscular weakness. It is believed to diminish pain and paraspinal muscle spasm, to reduce intradiscal pressure and to prevent gross body motion. Bracing may be helpful for patients who have poor muscular endurance or thoracic kyphosis. It may allow the patient to tolerate natural healing and avoid further invasive intervention. However, existing control studies do not provide convincing evidence for the effectiveness of bracing in patients with vertebral fractures whether non-operatively or operatively treated (286). There was no consistent difference between the intervention groups and the control group with regard to self-reported back pain, disability, returning to work, pain and muscle tension on clinical examination, progression of vertebral narrowing, gibbus or scoliosis. However, control studies were retrospective, not randomized, not blinded and only assessed patients with stable vertebral fractures. Indications for bracing, time of wearing a brace, co-interventions and follow-up time varied between the studies. Compliance, dropout rate and potential complications (skin defects, discomfort, emotional stress) were not assessed.

Thus, the value of bracing in patients with vertebral fractures remains unclear, and should be considered on an individual basis, as some may benefit whereas others may not. For every patient, the decision has to be taken on a case-to-case basis and include not only indications but also affordability and body habitus which may compromise the fit of the brace (e.g. in obese subjects). The brace design should be considered carefully, particularly in patients with rheumatoid arthritis who may have trouble using their hands to secure the brace properly.

Local steroid injections

Patients with intractable radicular symptoms may be considered for epidural steroid injections at the level of the symptoms. These injections should be performed under fluoroscopic guidance and should be correlated with imaging findings.

Vertebroplasty and kyphoplasty

Vertebroplasty refers to a transpedicular or parapedicular injection of polymethylmetacrylate (PMMA) into the fractured vertebral body (287-288). In kyphoplasty, the injection of PMMA is preceded by creation of the void in the vertebral body by inflating a balloon. These

procedures are performed under fluoroscopy in aseptic conditions, with sedation and local anesthesia.

There are two main indications for vertebro- and kyphoplasty (289):

1. a compression osteoporotic vertebral fracture resulting in an intractable, debilitating pain, refractory to medical management or necessitating high doses of analgesics causing severe side effects;

2. osteolytic changes of the vertebral body due to primary or secondary bone tumor provoking severe pain and vertebral instability.

Extreme vertebral collapse may make access to the vertebral body challenging. It is crucial to ensure that the patient's pain results from the fracture and not from other abnormalities. Active local or systemic infection as well as signs of retropulsion of a fragment of posterior wall or of the spinal disc into a spinal canal are strict contraindications. Coagulopathy must be corrected and drugs decreasing blood coagulation withdrawn before the procedure. Symptoms related to nerve root compression or central canal stenosis are relative contraindications.

Both vertebroplasty and kyphoplasty have been shown to decrease pain within several hours after the procedure, improve physical mobility and quality of life, and prevent prolonged immobilization (290-291). Thermal damage of nerve endings by polymerizing PMMA (~80°C) may induce rapid pain relief, whereas PMMA restores vertebral stiffness and provides an internal splint. However, it is also important to note that most vertebral fractures heal without surgical intervention and that pain, muscular contraction, and disability associated with a vertebral fracture decreases progressively with time. Evaluation of the efficacy of vertebro- and kyphoplasty is hampered by the use of the subjective criteria for efficacy measures, and paucity of placebo-controlled trials, which is particularly important as the placebo effect of the operating room conditions is substantial.

Thus, the results of observational studies and even of many controlled studies (not blinded, randomized or not, not standardized) should be interpreted cautiosly despite rapid pain relief and clinical improvement (292-299)**.** The differences in the functional outcomes between the groups (surgical vs conservative therapy) may be dramatic over the first days after therapy, but they progressively decrease to become non-significant after several weeks or months (299-300).

Only two double-blind, placebo-controlled studies have assessed the efficacy of vertebroplasty (301-302). Simulation of vertebroplasty corresponded to placebo. The authors

made a substantial effort with respect to blinding, including a sham procedure with local anesthetic injection but no vertebral augmentation. During the follow-up, there were no differences between groups in any of the investigated outcomes, including pain, disability, mobility, quality of life, and analgesic use.

Several criticisms have been voiced concerning these studies (303-306). Vertebroplasty appears to induce the greatest improvement in cases of a recent spine fracture and severe pain. However, in both the studies, enrollment was not restricted to recent fractures. Also, patients with acute fractures and most severe pain could decline to take the risk of being randomised into the placebo group, making selection bias possible. Other criticisms included the reliability of the clinical tools used for assessment of outcomes, insufficient statistical power, and the lack of systematic use of MRI for assessing the fracture status prior to the intervention.

Patients treated with vertebro- or kyphoplasty have a high incidence of subsequent vertebral fractures (307-308). Of particular concern are fractures that occur 30 to 60 days after the treatment in the vertebrae adjacent to the initial fracture (307-309). The risk of early adjacent level fracture following vertebroplasty is inreased in steroid-induced osteoporosis (310). It is not known whether these fractures are due to the patient's underlying osteoporosis, or whether the procedure itself alters vertebral mechanics, predisposing adjacent vertebral to fracture. Biomechanical studies have demonstrated that PMMA treatment alters the load transfer in the adjacent levels, leading some to speculate that this increases fracture risk in adjacent vertebrae (311). Additional research is needed to determine the optimal technique and target patient population to maximize the risk-benefit ratio of these procedures.

A frequent complication of vertebro- and kyphoplasty (50% of cases) is PMMA leakage (312-313). The leakage into the epidural space or the central canal may induce neurological deficits. The leakage of PMMA through a neuroforamen may induce a nerve root compression and radiculopathy, which, in very rare cases (<1%), may necessitate surgical decompression. In patients with central stenosis or radiculopathy, PMMA injection may exacerbate nerve compression. The leakage of cement into the veins draining vertebral body or its casual intravenous injection may result in pulmonary embolism (<0.5% of cases). Other risks comprise fractures of transverse processes and pedicles and pneumothorax. High temperature during PMMA polymerization may induce thermal damage of adjacent tissues and exacerbation of pain. Less frequent complications include hematomas, wound infections, allergy to injected substances and cardiopulmonary diseases related to anesthesia.

Summary

Bed rest, pharmacological treatment including opioids or non-steroidal anti- inflammatory drugs, mild physiotherapy and bracing should be considered when managing patients with vertebral fractures. Vertebral augmentation appears to provide rapid pain relief, though long term efficacy appears similar to conservative management of fractures. Thus, vertebral augmentation must be considered carefully, and while it may be appropriate for some individuals with intractable pain, additional studies are needed to better understand the patient population that will most benefit from this procedure.

VIII. Therapeutic decisions

The basis of the therapeutic decision is the fracture probability assessed from evaluation of clinical risk factors jointly, if possible, with BMD measured by DXA. It is necessary to exclude other cuases of low BMD which should be treated, e.g. osteomalacia or primary hyperparathyroidism. The potential causes of secondary osteoporosis should be evaluated and treated if possible, e.g. thyrotoxicosis or multiple myeloma. Analysis of modifiable lifestyle factors should not be neglected, e.g. smoking, alcohol abuse, nutritional habits. The patient should be informed that these factors also influence her/his bone fragility. The choice of medication depends on the drugs which are available in the country, their reimbursement, personal preferences of the patient and contraindications.

Prevalent vertebral fractures should be considered as a strong indication for anti-osteoporotic treatment except for high trauma fractures which are not related to low BMD and increased bone fragility. Other causes, such as malignancy, should be excluded before the prescription of anti-osteoporotic treatment. Bone protective treatment should be considered in all patients with fragility vertebral fractures for three reasons. Firstly, these fractures indicate general bone fragility. Secondly, the risk of further fractures is greatly increased, especially in the first year after the vertebral fracture (about 20%). Thirdly, there are therapies which can reduce the incidence of future fractures by 30 to 70%.

In patients with low trauma fractures at other sites, DXA measurement of BMD is indicated although in elderly patients, particularly those with hip fractures, bone protective therapy may be advised without the need for BMD measurement. If BMD is normal, other causes of low trauma fracture should be searched for, e.g. malignancy or fibrous dysplasia. If

BMD is in the osteoporotic range, the patient should be treated. If BMD is in the osteopenic range, the decision should depend on the type of fracture (all hip fractures should be treated, while fractures of the toes and fingers are usually non-osteoporotic), age, additional risk factors and current BMD. Risk of fracture doubles for every decrease in BMD of one standard deviation, thus, a T-score of -2.45 does not denote the same fracture risk as a T-score of -1.05 although both are in the osteopenic range.

In older postmenopausal women without a history of low trauma fracture who meet the WHO criteria for osteoporosis (T-score < -2.5 at the hip and/or spine), the risk of fracture is high enough to justify treatment after exclusion of other causes of low BMD. In the case of osteopenia (-1 < T-score ≤ -2.5), prevention of osteoporosis can be considered if there are other clinical risk factors. FRAX® is very useful for the evaluation of fracture risk in osteopenic women, especially, in younger ones. In elderly women, specific factors should be taken into account, e.g. high risk of falls, frailty, institutionalization, very low exposure to sunlight, very low physical activity. In this group, vitamin D and calcium supplementation are of particular importance. Preventing the first fracture is critical, as studies show that once a woman suffers a first vertebral fracture, the risk of developing a new fracture increases two- to five-fold.

Adherence and compliance to osteoporosis therapies

In the therapy of chronic diseases, three terms are defined: adherence, persistence and compliance. Persistence refers to the period during which the patient was taking the drug. A patient, who stopped taking a chronic therapy after 1 month, was not persistent. Adherence refers to the proportion of days covered i.e. when a patient was taking the drug compared with the number of days he/she should take it. A patient, who took strontium ranelate two or three times a week for 5 years, was persistent but not adherent (this drug should be taken every day). Compliance refers to taking the medication according to the specific indications for the drug. For instance, a patient who took 10 mg alendronate at the end of the lunch with a glass of milk every day for 5 years, was adherent and persistent but not compliant.

Currently, the most important problem of anti-osteoporotic treatment appear to be both poor adherence to and poor persistence with the treatment. Many studies show that only about 40 % of osteoporotic patients take the treatment for more than one year and about 20 % of patients take the treatment for 2 years (314-315). Analysis of adherence also shows that it is

often suboptimal (316). This is a serious clinical problem because the anti-fracture efficacy is strongly related to adherence (317-318).

Treatment of osteoporosis does not improve symptoms due to existing fractures and may cause side-effects. The precision error of DXA devices is relatively high compared with the change in BMD induced by the treatment. Therefore, at least two years of treatment are necessary before the effect of the therapy on BMD can be assessed at the individual level. Calls by the nurse of the physician prescribing the treatment or patient support programmes improved the persistence with the treatment with risedronate and ibandronate, respectively, at least during the first year (169, 319). During anti-resorptive treatment, a short term decrease (3 to 6 months) in BTM levels was inversely correlated with the long-term increase in BMD (2 to 3 years) at various skeletal sites (320). Thus, the use of the BTM has been proposed as a tool for monitoring anti-osteoporotic therapies and cutoffs for decreases for various BTM have been published (167). More recent studies show that the short term decrease in the BTM levels was associated with a greater anti-fracture efficacy (321-322). A substantial decrease in the bone resorption marker level during the anti-osteoporotic treatment was associated with an improvement of persistence (168-169). However, these data remain preliminary and more studies are needed to establish which methods improve compliance during anti-osteoporotic treatment.

Figure 1. Age-specific and sex-specific incidence of osteoporotic fractures. Adapted from Sambrook and Cooper (2006) Lancet 367: 2010
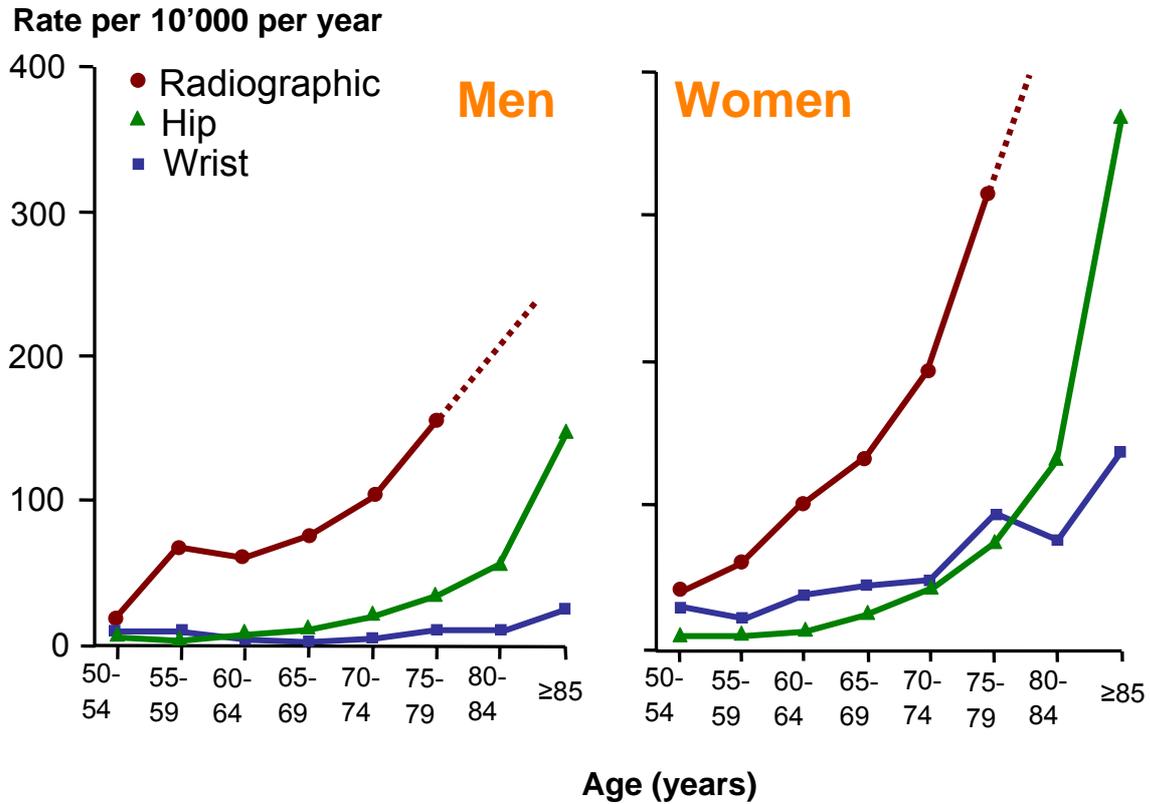

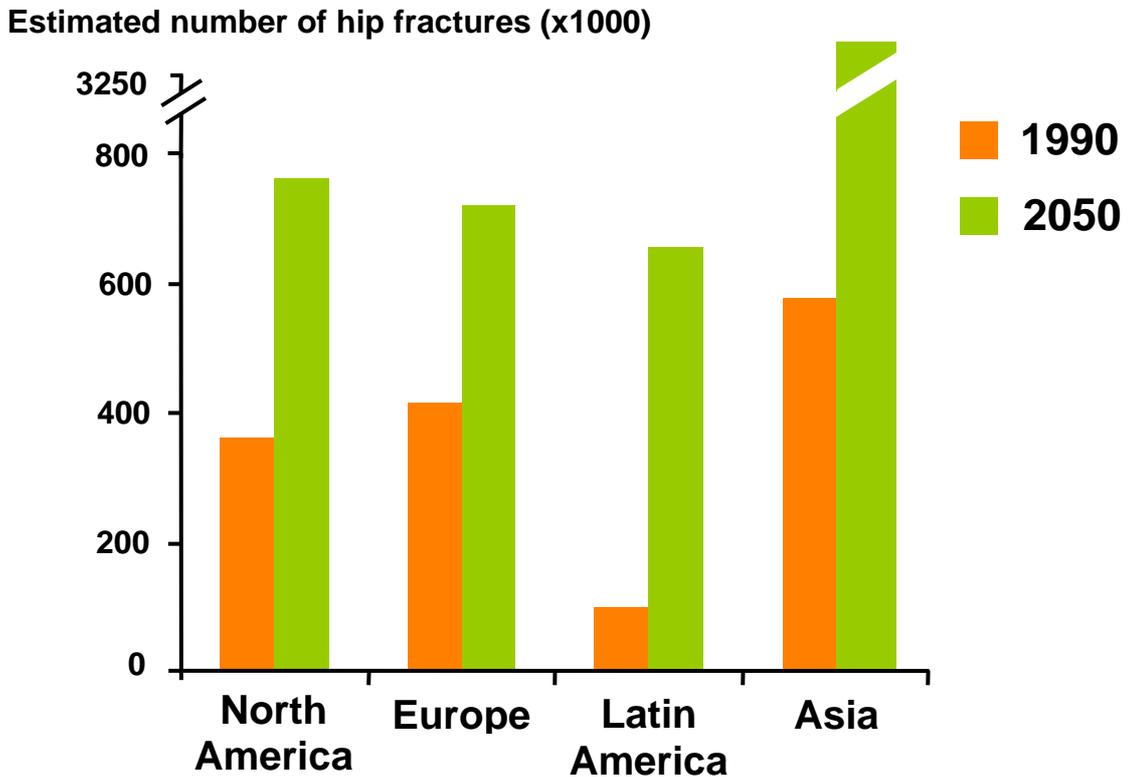**Figure 2.** Increased burden of osteoporotic fractures worldwide [18]

Figure 3. Prior fracture increases the risk for future vertebral fracture, independent of bone mineral density. BMD Tertiles (Low ▮ ; Middle ▮ ; High ▮) [60]

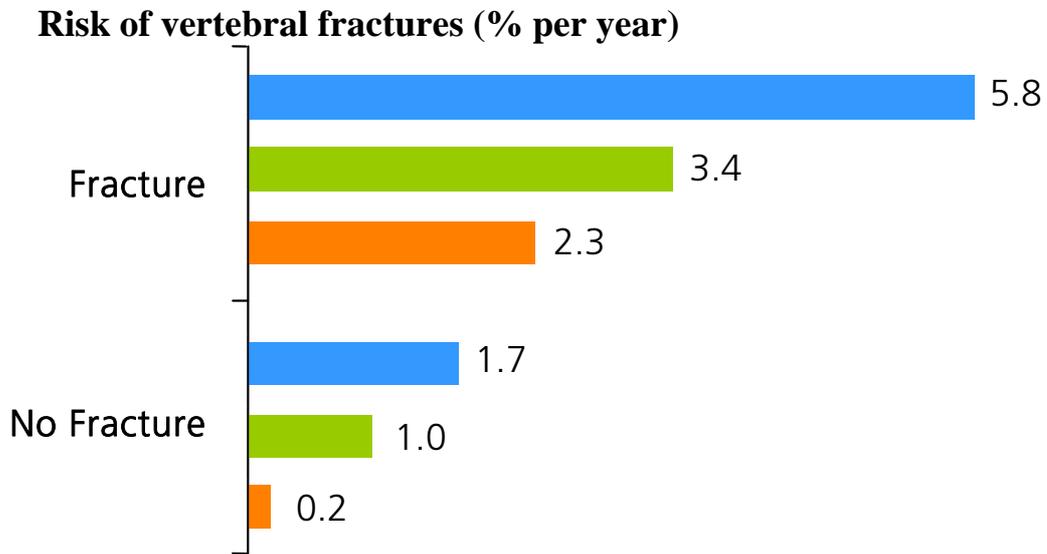**Risk of vertebral fractures (% per year)**

Figure 4. Relative risk of death following clinical osteoporotic fractures. Data from the Fracture Intervention Trial (FIT) that included 6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years [73].
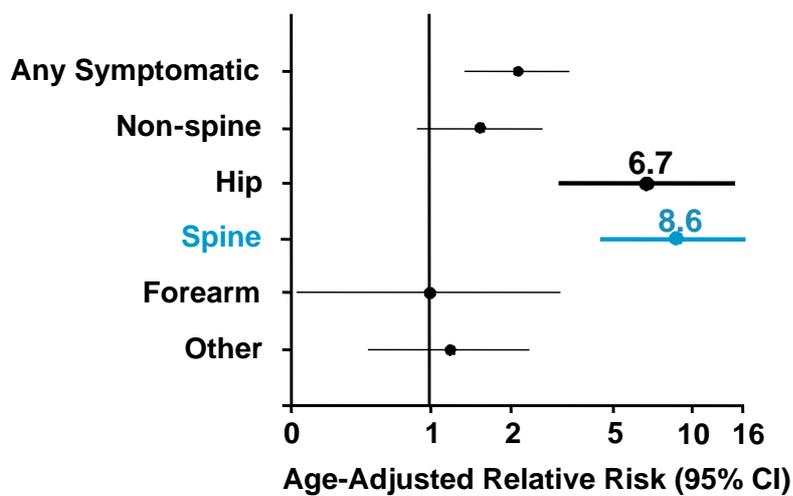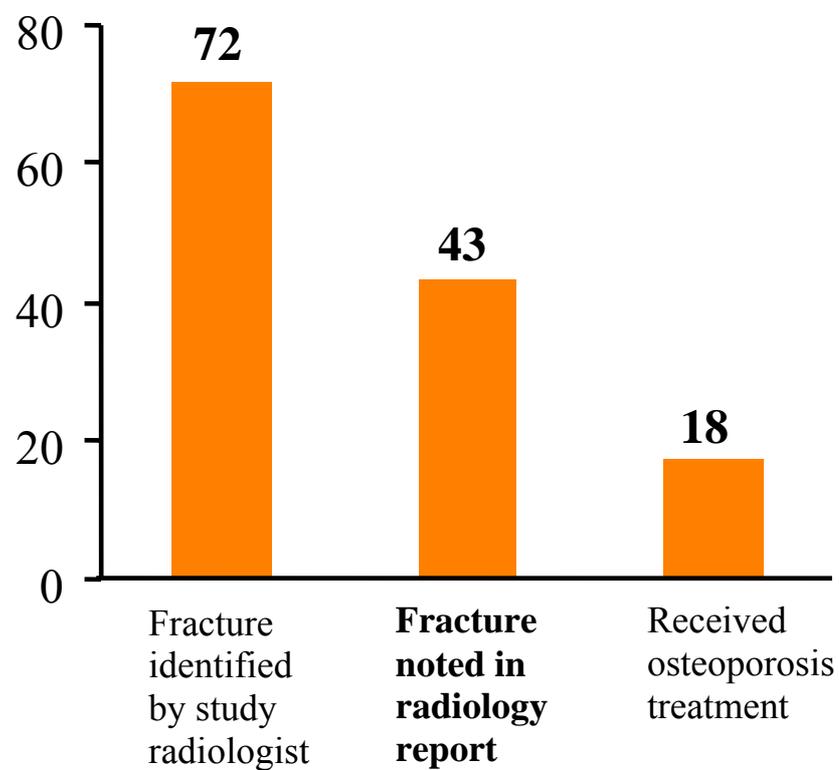
Figure 5. Under-diagnosed vertebral fractures – a study of 459 elderly patients [83]

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