

Bone fractures after menopause

The ESHRE Capri Workshop Group[†]

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BACKGROUND: Every year 30% of individuals above age 65 fall, and falls are the principal cause of bone fractures. To reduce fracture incidence requires both prevention of falls and maintenance of bone strength.

METHODS: PubMed searches were performed, for studies of the epidemiology of fractures, bone physiology, endocrine effects, osteoporosis measurement, genetics, prevention and effectiveness. Topic summaries were presented to the Workshop Group and omissions or disagreements were resolved by discussion.

RESULTS: Ageing reduces bone strength in post-menopausal women because estrogen deficiency causes accelerated bone resorption. Bone mineral density (BMD) decreased more than 2.5 standard deviation below the mean of healthy young adults defines osteoporosis, a condition associated with an increased risk of fractures. Risk factors such as age and previous fracture are combined with BMD for a more accurate prediction of fracture risk. The most widely used assessment tool is FRAXTM which combines clinical risk factors and femoral neck BMD. General preventive measures include physical exercise to reduce the risk of falling and vitamin D to facilitate calcium absorption. Pharmacological interventions consist mainly in the administration of inhibitors of bone resorption. Randomized controlled trials show treatment improves BMD, and may reduce the relative fracture risk by about 50% for vertebral, 20–25% for non-vertebral and up to 40% for hip fractures although the absolute risk reductions are much lower.

CONCLUSIONS: Although diagnosis of osteoporosis is an important step, the threshold for treatment to prevent fractures depends on additional clinical risk factors. None of the presently available treatment options provide complete fracture prevention.

Key words: falls / bone fractures / osteoporosis / ageing / bone mineral density

Introduction

Fractures in major bones occur more often in later life and are associated with considerable morbidity and mortality (Johnell and Kanis,

2006; Compston *et al.*, 2009). Fractures in fragile bones are associated with osteoporosis, a skeletal disease characterized by low bone mass and impaired bone structure, leading to bone fragility and increased fracture risk (Sambrook and Cooper, 2006). The most frequent

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osteoporotic fractures are those of the vertebrae, lower forearm and hip. Vertebral fractures are not always clinically evident, but fractures of the lower forearm and hip are painful with loss of limb function and fractures of the hip require hospitalization (Kanis *et al.*, 2008a). The ultimate cause of limb fractures is usually a fall and falling is more common in the elderly, which means that any strategy to prevent fractures must address not only bone strength but also the tendency to fall (Petridou *et al.*, 2008).

The first step in prevention protocols is the diagnosis of osteoporosis by measurement of bone mineral density (BMD); when osteoporosis is present, whether treatment is indicated depends on the level of fracture risk, which varies with age and other factors. Treatment options for women, at least prior to the Women's Health Initiative (WHI) study, included hormone treatment (HT). The WHI study confirmed that, even in women who were not at high risk, estrogen alone or with progestin significantly reduced fracture rates (Cauley *et al.*, 2003; Anderson *et al.*, 2004). The effect was small, however, because women aged 50–60 years who were most likely to use HT have a low risk of fracture. In addition, cardiovascular and cancer adverse events were more numerous than the hip fractures prevented.

HT of menopause is no longer recommended for fracture prevention and the majority of osteoporosis treatments now involve drugs with specific effects on bone. As a result, clinicians not in the field of reproductive medicine, rather than gynecologists are involved in this treatment. Nevertheless, women coming to gynecology and menopause clinics remain concerned about osteoporosis and its risks. The purpose of this review, therefore, is to provide their clinicians with information to guide patients in their choices. The review covers the burden of illness, bone physiology and treatment strategies.

Methods

Searches were done in Medline and other databases by individual participants in the Workshop about epidemiology of falls and fractures, bone physiology, endocrine effects on bone physiology, genetics of bone strength, osteoporosis measurement, non-pharmaceutical and pharmaceutical prevention and their effectiveness. Selection criteria were (i) highest quality studies: prospective cohort studies for diagnosis and prognosis, and randomized controlled trials (RCTs) for prevention and treatment; and (2) studies most relevant to clinical practice involving female patients. Each subject summary was presented to the Workshop Group where omissions or disagreements were resolved by discussion.

Frequency of falls

Falling, not osteoporosis, is the strongest single risk factor for fractures in elderly individuals. Although a one standard deviation (1 SD) reduction in BMD increases the fracture risk by up to 2.5 times, a sideways fall increases the risk of hip fracture by three to five times (Järvinen *et al.*, 2008).

A fall is 'an unexpected event in which the participant comes to rest on the ground, floor or lower level' (Lamb *et al.*, 2005). When a person falls, the type and severity of the fall is likely to determine whether a fracture occurs. The type of fall is defined by the direction and the associated energy. The severity of a fall reflects the distance fallen or the height from which the fall occurs.

In a community of 409 people aged 65 years, each year 30% had a fall, and older women (above age 80) had a 30% increased risk of falling as compared with older men (O'Loughlin *et al.*, 1993). Many falls are non-injurious, but one in five falls among senior citizens may require medical attention and about 1 in 20 falls result in a fracture; these rates are doubled above the age 75 years (Kannus *et al.*, 2005).

Falls cause a large burden of disease and disability among senior citizens and are costly to health services. Half of the deaths due to injury in older people in the European Union (EU) are a consequence of a fall, resulting in about 40 000 deaths each year (Petridou *et al.*, 2008). In the year 2000 the total cost of unintentional falls in older people in the UK was estimated to be about £1 billion (GBP) (Scuffham *et al.*, 2003).

Mortality rates from falls differ widely within the EU, with a 10-fold variation between the highest rates observed in Hungary and the Czech Republic, and the lowest rates in Bulgaria, Spain and Greece (Petridou *et al.*, 2008). Mortality rates from falls among the elderly in most European countries have declined from the early 1990s to the early 2000s, although increases in rates have been noted in a few countries, such as Finland, Ireland and Latvia (Petridou *et al.*, 2008). Some of the differences in rates may reflect different certification practices between countries.

Prevalence of fractures

In the year 2000 the number of clinically evident fractures in women worldwide was estimated to be 5.5 million, of which 1.1 million were at the hip, 1.3 at the forearm, 0.9 at the spine, 0.5 at the humerus and 1.9 at other sites. For total fractures and for hip fractures, the peak age was between 75 and 79 years (Johnell and Kanis, 2006).

The estimated prevalence of osteoporotic fractures worldwide in women above age 50 years was around 35 million, of which 13.9 million were in Europe, 9.0 million in the Western Pacific, 6.4 million in the Americas, 4.5 million in Southeast Asia, 0.8 million in the Eastern Mediterranean and 0.2 million in Africa (Johnell and Kanis, 2006).

At age 50 years the lifetime absolute risk of hip fractures in women was 7% in a study from Australia, 15% in a study from the USA and ranged between 11 and 30% in five studies from Europe (Ahmed *et al.*, 2009). Lifetime risk of osteoporotic fractures lies within the range of 40–50% in women and 13–22% in men (Johnell and Kanis, 2005).

Adult bone remodeling

Bones have a complex anatomy (Fig. 1) and provide structural support for muscle attachments and act as a reservoir for the storage of calcium and phosphate in the regulation of mineral homeostasis.

The process of bone remodeling is responsible for renewal and repair of the skeleton during adult life (Fig. 2). Bone remodeling starts with attraction of osteoclast precursors to the target site, probably by local release of chemotactic factors from areas of microdamage. The osteoclast precursors then differentiate into mature osteoclasts and attach to the bone surface by forming a sealing zone. The osteoclasts then secrete hydrochloric acid and proteolytic enzymes including cathepsin K into the space underneath the sealing

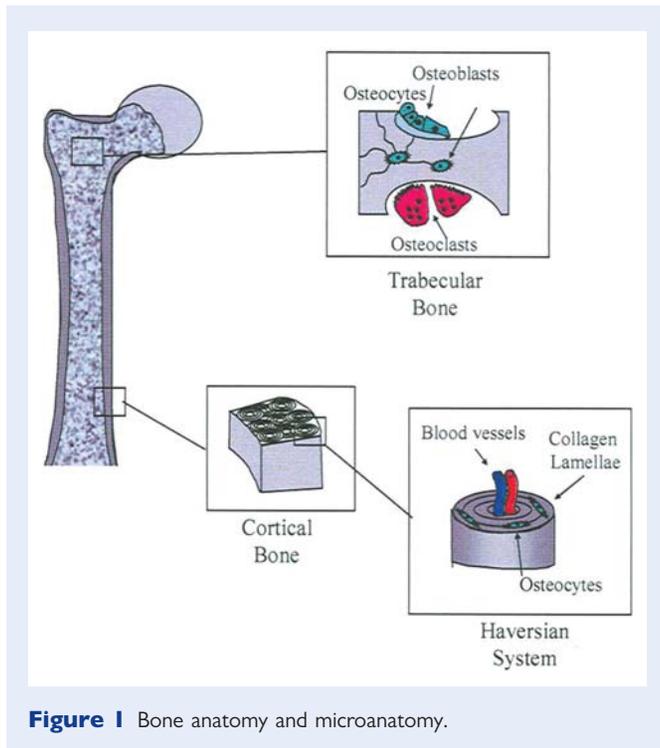


Figure 1 Bone anatomy and microanatomy.

zone. In the process of bone resorption the acid dissolves the mineral and the cathepsin K degrades bone collagen. When resorption is complete, osteoclasts undergo programmed cell death and bone formation begins with the attraction of osteoblast precursors to the resorption site. The osteoblast precursors differentiate into mature osteoblasts which deposit new bone matrix in the resorption lacuna, until the hole is filled. Some osteoblasts become trapped in bone matrix and differentiate into osteocytes. Osteocytes act as biomechanical sensors and produce several molecules that influence bone remodeling and phosphate metabolism including sclerostin (SOST), fibroblast growth factor 23 (FGF23) and dentin matrix acidic phosphoprotein 1 (Dmp1) (Bonewald and Johnson, 2008).

In normal individuals, bone mass increases during skeletal growth to reach a peak at the beginning of the third decade and at this point

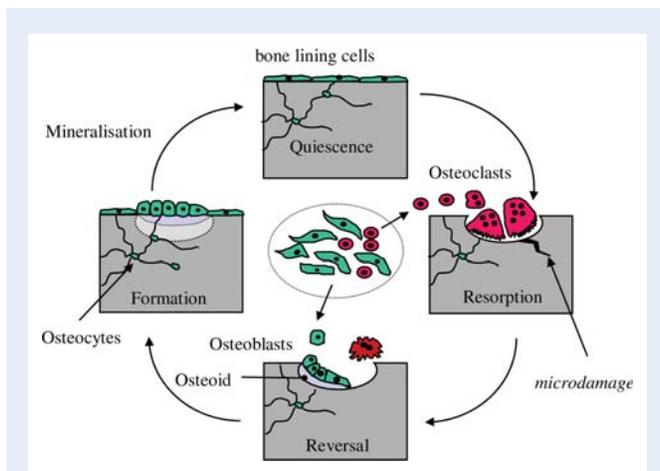


Figure 2 The bone remodeling cycle.

bone resorption and formation are equally balanced. Levels of peak bone mass are strongly influenced by genetic factors although diet and exercise also play a role (Ralston and de Crombrughe, 2006). After the age of about 45 bone mass falls, particularly in women due to an accelerated phase of bone loss which occurs as the result of estrogen deficiency at the menopause. The estrogen deficiency causes imbalance between bone resorption and bone formation, such that the amount of bone removed during the remodeling cycle slightly exceeds that which is replaced. With increasing age there is a reduction in bone turnover from that observed immediately after the menopause, although values remain higher than in premenopausal women. With advancing age there is also a tendency for fat cells (adipocytes) to accumulate in the bone marrow and this is thought to be due to an age-related reduction in the ability of bone marrow stromal cells to differentiate into osteoblasts and an increase in their ability to differentiate into fat cells. It is of interest that rosiglitazone and related compounds promote adipocyte differentiation at the expense of osteoblast differentiation and predispose to osteoporosis through this mechanism (Lazarenko et al., 2007).

Several circulating hormones including parathyroid hormone (PTH), estrogen and 1,25-dihydroxyvitamin D, regulate bone remodeling. These hormones have direct effects on bone cells but also act by regulating local production of mediators in the bone micro-environment such as cytokines and growth factors, which then regulate bone cell activity.

The most important mediators of osteoclast activity are receptor activator of nuclear factor kappa B (RANK), RANK ligand (RANKL) and Osteoprotegerin (OPG) (Hofbauer et al., 2000). Bone resorption is stimulated by RANKL, which binds to RANK and causes osteoclast activation by up-regulating nuclear factor kappa B (NFκB) and other signaling pathways. This process is blocked by osteoprotegerin which acts as a 'decoy' receptor for RANKL (Fig. 3). It is already available one new pharmaceutical, denosumab, is a human monoclonal antibody to the RANKL that blocks its binding to RANK, thus inhibiting the development and activity of osteoclasts and thereby decreasing bone resorption (Cummings et al., 2009).

Bone formation is regulated by many factors including PTH, bone morphogenic proteins (BMP) and molecules in the *Wnt* signaling pathway. PTH promotes osteoblast differentiation and stimulates proliferation of osteoblast precursors, whereas BMP promote differentiation of osteoblast precursors to form mature osteoblasts. There are at least 19 members of the *Wnt* family and in particular *Wnt7b* and *Wnt10b* play a role in regulating bone formation (Krishnan et al., 2006) by activating lipoprotein receptor-related protein 5 (LRP5) which together with *Frizzled* forms a receptor for *Wnt* family members. Binding of *Wnt* causes activation of the LRP5 pathway which stimulates bone formation by increasing levels of beta-catenin within the osteoblast (Johnson et al., 2004). Activation of LRP5 signaling in osteoblasts also inhibits bone resorption by increasing production of osteoprotegerin (Glass et al., 2005). A variety of inhibitors of LRP5 signaling have also been identified, including soluble Frizzled-Related Proteins (sFRP), Dickkopf (Dkk) and SOST and it is likely that regulation of bone formation depends on the balance between levels of the stimulatory *Wnt* molecules and levels of the inhibitors such as sFRP and SOST. Sclerostin is of particular interest since it is produced by osteocytes in response to mechanical loading and probably acts as a mediator of the effects of mechanical

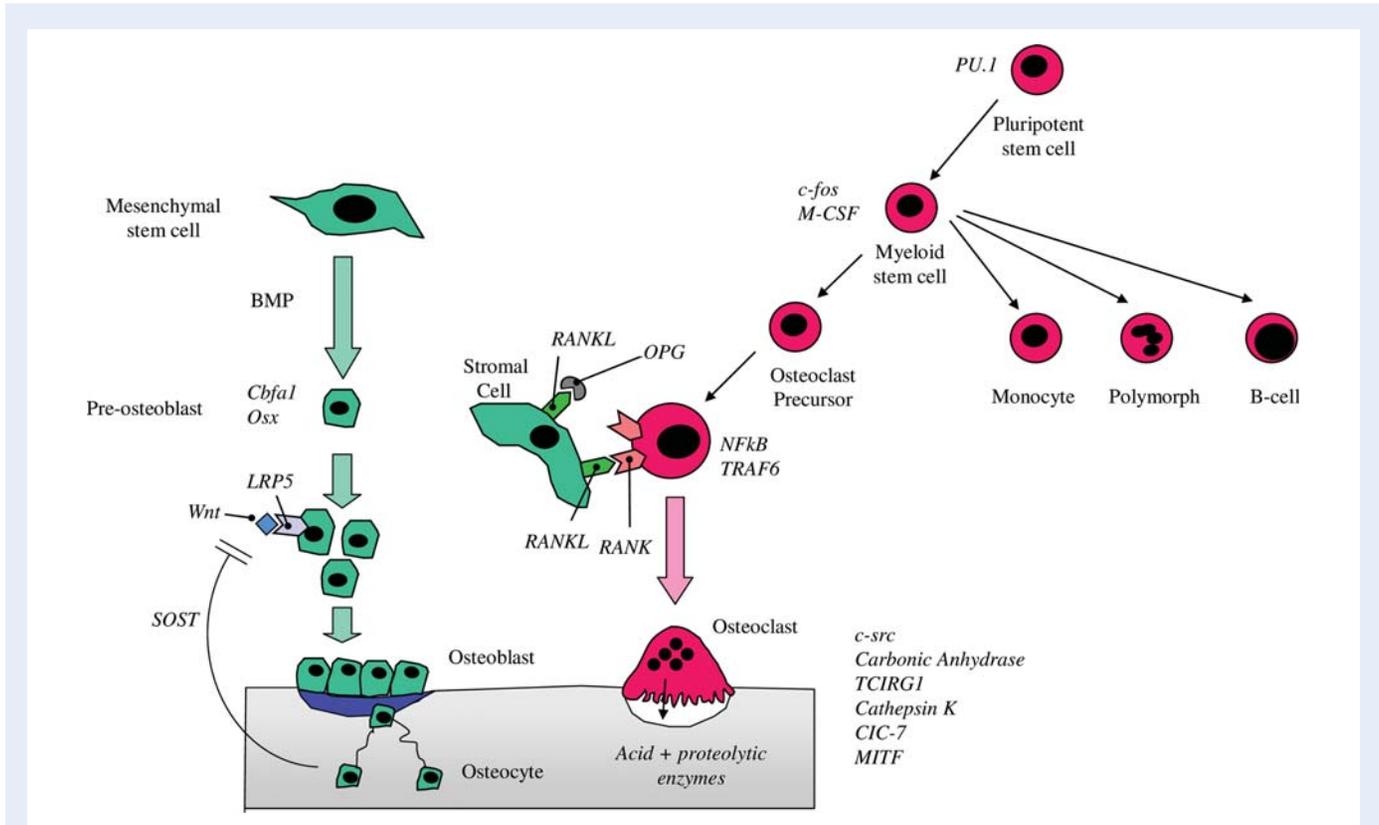


Figure 3 Key regulators of osteoblast and osteoclast function. Great proportion of the RANKL is present in a free form and is produced by different types of cells.

loading on the skeleton (Robling *et al.*, 2008). Recent research has also shown that various other pathways play a role in regulating bone mass and bone turnover including the sympathetic nervous system through production of catecholamines (Takeda *et al.*, 2002), serotonin, acting on the 5-hydroxytryptamine (serotonin) receptor 1 b (Htrb1) receptor which is expressed on osteoblasts (Yadav *et al.*, 2008) and by cannabinoids, acting through the type 1 (CB1) and type 2 (CB2) receptors (Ildris *et al.*, 2005; Ofek *et al.*, 2006; Ildris *et al.*, 2009) and by nitric oxide which regulates the effects of proinflammatory cytokines and estrogens on the skeleton (Van't hof *et al.*, 2000; Armour *et al.*, 2001).

Thus, there are several determinants of bone remodeling (Table I) and the process is regulated through a variety of pathways (Table II), which provide multiple therapeutic targets for the prevention and treatment of bone disease.

Ovarian hormones and bone metabolism

As suggested in the 1940s by Albright and Reifstein, ovarian hormones play a pivotal role on bone development and homeostasis. The consequences of natural reduction in sexual steroid hormone levels cause decreased mineralization and increased bone resorption. In men and women, estrogens play the most important role in this change, as evidenced by the remarkable effects of estrogen therapy in post-menopausal women, which reduces bone resorption and decreases the fracture rate (Cauley *et al.*, 2003). Although some

evidence suggests that androgens can influence bone expansion, studies in knockout mice as well as the description of women and men with abnormal estrogen metabolism, such as CYP 19 aromatase deficiency, androgen insensitivity and low estrogen production, indicate that estradiol is the key regulator of bone growth and maintenance (Syed and Khosla, 2005). Estrogens indeed control the balance between osteoblasts the bone matrix forming cells and bone-resorbing osteoclasts. Further, recent findings suggest that locally produced estrogens may contribute to the turnover and function of bone tissues independently of systemic estrogens (Li *et al.*, 2009).

Table I Key determinants of peak bone mass and bone loss.

Peak bone mass	Bone loss
Genetics (70–80%)	Sex hormone deficiency
Body weight	Body Weight
Sex hormones	Genetics
Diet	Diet
Exercise	Immobility
	Diseases
	Drugs (among others): Corticosteroids, Aromatase inhibitors, Glitazones

Table II General and local regulators of bone turnover.

General factors	Mechanical
	Exercise
	Bed rest
	Neurogenic
	Leptin/adrenergic
	Nitric oxide
	Cannabinoids
	Hormonal
	Calcitonin
	Sex hormones
	PTH/1,25 vitamin D
	Thyroxine, TSH, GH/IGF
	Corticosteroids
Local factors	Osteoclasts
	RANK, RANKL, OPG
	IL-1, TNF, IL6, TGF β
	Nitric oxide, Cannabinoids
	Osteoblasts
	Wnt/LRP-5/SOST
	TGF β /BMP
Nitric oxide	

Estrogens act mainly through nuclear ligand activated–receptors, essentially estrogen receptor ER α and also ER β which bind to specific response elements on the promoters of specific genes. Interestingly, 30% of estrogen regulated genes do not have estrogen response elements and this suggests they are activated by indirect mechanisms through other transcription factors.

Non-genomic effects of estrogens have been well described; these very rapid mechanisms are mediated by membrane receptors, and activation of kinases which modulate intracellular calcium and cAMP levels, and/or activation of MAP kinases and inositol phosphate-3 kinase pathways.

ER α and ER β are expressed in a pleiotropic manner, and in particular in the bone and cartilage (Venken *et al.*, 2008; Tanko *et al.*, 2008). Their expression has been characterized in osteoblasts, osteoclasts, osteocytes, chondrocytes, as well as in bone medulla. ER α is mostly present in cortical bone and is mainly involved in bone differentiation.

Estrogens affect precursors of osteoblasts and osteoclasts which increase their number following castration in mice. Osteoclast differentiation involves the activation of several transcription factors such as M-CSF, RANKL and osteoprotegerin. All these factors are modulated by estrogens. In addition osteoblast apoptosis is inhibited by estrogens.

Finally, estrogens regulate formation, activity and half life of osteoclasts. This effect explains the increase in bone resorption observed after menopause. In this context, interleukin-1 (IL-1), tumor necrosis factor α (TNF α) and interleukin-6 (IL-6), play an important role in the bone loss following menopause, since their production by osteoblasts is inhibited by estrogens.

These complex mechanisms through which estrogens regulate bone resorption and formation, are of paramount importance in health care as evidenced by the remarkable effects of estrogen therapy in women with inactive ovaries. In addition, the application of selective estrogen receptor modulators (SERMs) to the treatment of osteoporosis, has

also been a crucial lead in our clinical armamentarium since SERMs can also decrease the risk of breast cancer, a classical limitation for the use of estrogens in aging women (Kung *et al.*, 2009).

ER α remains the key mediator of estrogen effects in bone, although the role of ER β in this tissue remains to be elucidated. As a consequence, ER β specific ligands do not prevent or treat osteoporosis. Progress is expected both to dissociate the bone effect of estrogens from their uterotrophic consequences and their effects on breast proliferation. The co-administration of SERMs and estrogens seems to be of great interest. Also, the characterization of all the molecular steps of estrogen action through transcription factors, and kinases, may help to find new therapeutic targets.

Relationship between BMD and fracture risk

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk. BMD, along with bone geometry, micro-structure and bone turnover are the determinants of bone strength (Seeman and Delmas, 2006a). The diagnosis of osteoporosis is based on the determination of areal BMD at the spine or proximal femur. Areal BMD accounts for two-thirds of the variance of the strength of isolated bone specimens. Besides bone mineral mass- and bone turnover-related variables, clinical risk factors can capture features of osteoporotic fracture risk above those provided by BMD and/or bone remodeling rate. No single symptom or sign can confirm or rule out osteoporosis. However, clinical features may have cumulative effects, and may be combined to provide a significant and meaningful estimate of fracture risk which can be used in a treatment decision strategy and in the definition of an intervention threshold (Kanis *et al.*, 2008a).

Femoral neck BMD appears to be a better predictor of fracture of the proximal femur, based on long-term prospective longitudinal studies with fracture as the outcome. Since femoral neck BMD is less influenced by osteoarthritis than spine BMD, it represents the most suitable measure for the diagnosis of osteoporosis in the elderly (Marshall *et al.*, 1996). Indeed, above the age of 65, spine can barely be considered for diagnostic purposes. Femoral neck BMD is the variable included in the WHO-FRAX[®] tool (Kanis *et al.*, 2007). Measuring several skeletal sites (spine, neck and total hip) may increase the prevalence of subjects with osteoporosis, but it does not improve the accuracy of fracture prediction.

A World Health Organization panel (1994) has proposed that BMD falling more than 2.5 SD below the mean values in healthy young adults is the diagnostic criterion for osteoporosis (*T*-Score). Its measure is made as follows: *T*-Score = (measured BMD – Young Adult BMD)/Young Adult SD. Ninety-five percent of the populations are included in ± 2 SD and 99% in ± 3 SD (Fig. 4). The fracture rate in the reference population of healthy young adults is very low. This approach to diagnosis is similar to the measurement of blood pressure for the diagnosis of hypertension. The *T*-score is a diagnosis threshold, which should clearly be distinguished from a therapeutic threshold. For the latter, other factors such as age, concomitant clinical risk factors, bone turnover and the benefits, side effects and cost of treatment should be considered as well (Kanis *et al.*, 2007).

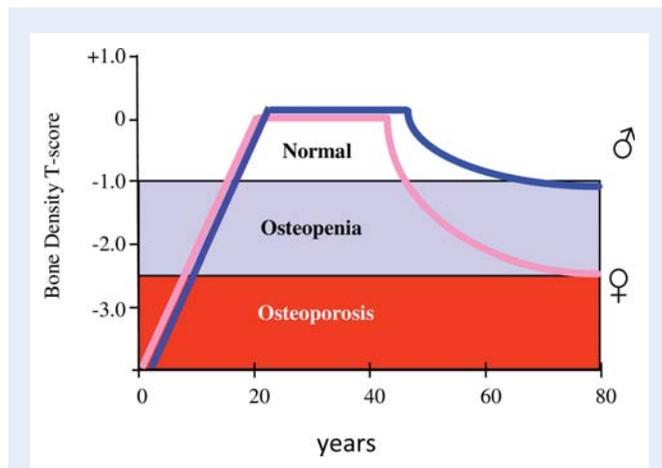


Figure 4 Changes in bone density *T*-score with age. *T*-score = (young adult BMD – measured BMD)/young adult SD. Osteopenia *T*-score between 1 and 2.5 SD. Osteoporosis *T*-score below 2.5 SD. Pink line, females; blue line, males.

The prevalence of subjects with bone mass values below the 2.5 SD threshold increases with age, reaching ~40% at the age of 80. The lifetime risk of any skeletal fracture in a 50-year-old woman depends on the incidence of fracture in the relevant population and on her life expectancy. For instance, in Switzerland, which has a prolonged life expectancy, lifetime risk of fracture is as high as 51.3% for a woman at the age of 50. For a man, due to the different bone diameter, this risk is 20% (Lippuner *et al.*, 2009). However, it should be remembered that there is no BMD threshold value for the risk of osteoporotic fracture, only that the relationship is characterized by a continuous increasing gradient of risk with the decrease of BMD.

Identification of women at risk

In white populations about 50% of women and 20% of men aged over 50 will have a fragility fracture in their remaining lifetime (Sambrook and Cooper, 2006). The consequences for the individual and the cost to the health service of fragility fractures are serious. A range of preventive treatments exists but as all treatments have some risks, side effects or drawbacks, it is important to select the people who most need treatment by identifying those at greatest risk of fracture.

The risk factors for fracture include: previous osteoporotic fracture (or a fracture associated with a low-trauma event) family history of hip fracture, having a fall and of course osteoporosis itself. Although there is long list of well-recognized risk factors for osteoporosis (Table III), osteoporosis is not the most important of the risk factors for fracture (Vaugh *et al.*, 2009).

Previous fracture

In a meta-analysis involving almost 45 000 women from 11 international cohorts followed for a total of 250 000 women-years, a history of previous low-impact/osteoporotic fracture almost doubled the risk of osteoporotic fracture (RR 1.86; CI 1.75–1.98) compared with women without a history of fracture (Kanis *et al.*, 2004). Impressively almost one in five women (19.2%) who develop

Table III Risk factors for osteoporosis (Vaugh *et al.*, 2009).

Not modifiable	Modifiable
Increasing age	Weight
Female sex	Smoking
Caucasian ethnicity	Alcohol
Age at menopause	Exercise
Family History	Diet

a vertebral fracture (the commonest osteoporotic fracture) will have another fracture within 1 year (Lindsay *et al.*, 2001). The effect on risk of a previous fracture may not be confined to low-impact fractures; in a study of women over 65, a previous high-trauma fracture was associated with 34% greater risk of subsequent fracture compared with women with no previous fracture (Mackey *et al.*, 2007).

Falls

Falls are associated with an increased risk of fracture, independently of osteoporosis. In a cohort study of over 40 000 older people in care homes falls increased the risk of hip fracture by 30% (Stolee *et al.*, 2009).

Osteoporosis

The lifetime risk of fracture at age 50 is 50% for any woman (Kanis *et al.*, 2007) and the risk of fracture almost doubles for each SD reduction in BMD (Johnell *et al.*, 2005). In the 1990s the measurement of BMD by Dual Energy X-ray Absorptiometry (DEXA) became the gold standard for assessing fracture risk. Other investigations are available for bone mass measurement, like quantitative ultrasound or quantitative computer tomography. Low ultrasounds-determined stiffness, which combines speed of sounds and broad band attenuation, predicts fracture risk similarly to DEXA-based BMD measurement. Biochemical markers evaluate bone turnover. However, BMD remains the major criterion used for diagnosing osteoporosis. Although BMD is a simple, quick, non-invasive and now relatively cheap investigation, many fractures occur in people who do not have a low BMD. Since not everyone who has osteoporosis will have a fracture, in most settings guidelines, based on known risk factors for osteoporosis, are used to decide who is eligible for BMD measurement.

Risk factors for osteoporosis

Non-modifiable risk factors include sex, age, family history and early menopause (Vaugh *et al.*, 2009) (Table III). Women have a lower total bone mass, they live longer compared with men and are, especially after the menopause, at increased risk of losing bone. Depending on lifestyle, men lose 0.0–0.9% of bone annually, women 0.9–1.2%. Age is a second non-modifiable risk factor: osteoporosis in Caucasian American women is 27% between 50 and 59, 32% between 60 and 69 and 41% over 70. Women with an early menopause should be considered at higher risk than women of the same age with late menopause. A family history (parents, sibs) of osteoporosis ('easily fracturing') contributes significantly to an

individual's risk (Soroko *et al.*, 1994). Individual BMD decreases as the number of family members with osteoporosis increases. Modifiable risk factors include lack of exercise, low body weight, inadequate diet, excess alcohol use and smoking (Law and Hackshaw, 1997; Vaughn *et al.*, 2009).

BMD guidelines

A host of recommendations for who should have BMD screening for osteoporosis have been produced by a variety of professional organizations (Lim *et al.*, 2009). In general, most guideline recommendations are based on age and sex with or without known clinical risk factors. The guidelines in the USA and Canada recommend screening all women aged 65 and older and all men aged 70 and older regardless of the presence of risk factors and also recommend screening of all post-menopausal women who have known risk factors. The more recent guidelines recommend using an osteoporosis screening tool. A number of these have been developed, the diagnostic accuracy of the best known tools was assessed among 7779 USA women aged 67 years. The osteoporosis self-assessment tool (OST) ($0.2 \times$ weight in kg minus age) had the greatest area under the receiver operating characteristic curve (AUC 0.76, 95% CI 0.74, 0.77). By itself, however, weight had an AUC of 0.73 (95% CI 0.72, 0.75), which was better than the values for other scores, age alone or prior fracture (Gourlay *et al.*, 2008).

Fracture prediction

Assessment of BMD captures only part of the fracture risk and lacks sufficient sensitivity for population screening; moreover other risk factors, particularly age, add important information about fracture risk (Fig. 5). Various attempts have been made to construct assessment tools which use clinical risk factors with or without BMD to predict fracture risk and thereby to set thresholds for preventive therapy (Lim *et al.*, 2009). The most widely used of these tools is FRAX™ which combines easily obtained clinical risk factors (body mass index, prior history of fracture, parental history of hip fracture, use of steroids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking and alcohol intake) with femoral neck

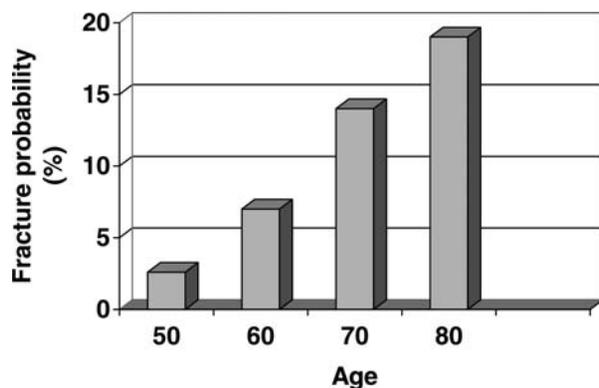


Figure 5 Relationship of 10 years fracture probability with age in women with comparable osteoporosis (BMD = -3 SD) (Sweden) (Kanis *et al.*, 2001).

BMD (Kanis *et al.*, 2008b). FRAX™ is internet based and can be adapted for use in different countries with varying prevalence of osteoporosis and fracture.

Genetic determinants of osteoporosis

A genetic contribution to the pathogenesis of osteoporosis, accounting for 50–80% of the inter-individual variability in bone mass and quality, has been demonstrated in twin and family studies (Torgerson *et al.*, 1996; Gennari *et al.*, 2002). Personal and family history predicts fractures in early post-menopausal women, an effect that decreases with age but does not disappear (Michaëlsson *et al.*, 2005). Genetic factors contribute to osteoporosis by influencing not only BMD, but also bone size, bone quality and bone turnover (Peacock *et al.*, 2002).

Given the complex biology of the skeleton, it is likely that bone mass is under the control of a large number of genes, many of which exert only minor effects on BMD, whereas a few may contribute substantially to variability in this trait. Among the numerous genes implicated in the etiopathogenesis of skeletal disorders such as osteoporosis, the most likely candidate genes are: those encoding for bone matrix protein synthesis, calcitropic hormones, sex hormone synthesis and metabolism and their receptors; and those encoding for cytokines, bone biomarkers and proteins responsible for hereditary bone disorders (i.e. low-density LRP5 and LRP6). These genes should be considered in the choice for segregation analyses of this multigenic disorder (Carbonell Sala *et al.*, 2005).

Osteoporosis is inherited as a Mendelian monogenic disorder only in rare bone diseases, although the common form of osteoporosis is multifactorial, arising from the interaction of polymorphic alleles with environmental and lifestyle factors interactions.

Lifestyle and dietary fracture prevention

Osteoporosis, dietary insufficiency, inactivity, senile sarcopenia and falls are all risk factors for fractures which may be modified by changes in lifestyle. Osteoporosis is a growing concern in a society that is characterized by a rapidly growing proportion of post-reproductive individuals. It affects both men and women of advanced age, although women four times more than men: one in three women over the age of 50 will suffer an osteoporotic fracture as compared with 1 in 12 men (Hannan *et al.*, 2000). Changing lifestyle habits contribute to the dietary and activity risks. The less active, more sedentary lifestyle of young people today has not only caused the present obesity epidemic, but it also will negatively impact future peak bone mass and decrease future bone reserve capacity. Diminished peak bone mass, together with the relative and absolute increase of elderly people in society, will lead to a rapid increase in future osteoporotic fracture case incidence. Currently, 50% of patients who have sustained a hip fracture are no longer able to lead an independent life and 25% die within 1 year.

Osteoporosis, sedentary life, falls and fractures are interrelated and it is difficult to identify individual contributing lifestyle risk factors within this evolutionary-social disease conglomerate. Non-modifiable risk factors cannot be changed, but prevention programs can be based

on the modifiable risk factors such as exercise, weight, diet and smoking (Law and Hackshaw, 1997).

Activity

An increased adolescent active lifestyle has been associated with increased BMD later in life. Past and current participation in active exercise programs both contribute to a higher post-menopausal BMD (Kemmler *et al.*, 2004). Conversely a sedentary adolescence and sedentary lifestyles are risk factors for osteoporosis. In contrast, among post-menopausal women, if exercise leads to a low body mass index, this is associated with low BMD and more rapid bone loss, and a consequent higher risk of developing osteoporosis (Forsmo *et al.*, 2009).

Exercise reduces the risk of falling, increases BMD and decreases fracture risk (Kelley *et al.*, 2001). General fall prevention activities and/or individually tailored fall prevention interventions significantly reduced falls from 2.54 to 2.09 falls per patient per year (Neyens *et al.*, 2009). Balance and gait training, appropriate use of walking devices, low-impact weight bearing exercises, muscular endurance training and high-intensity strength training maintain BMD both in elderly men and women. Regular walking promotes bone health (Schmitt *et al.*, 2009). Although increased physical activity may improve osteoporosis and reduce the likelihood of falls, an impact on fracture prevention has not yet been shown.

Diet

High lifetime dietary dairy product intake has been associated with decreased osteoporosis risk later in life, although many of the reports on diet and osteoporosis risk are not high quality and do not reach firm conclusions. Nevertheless, healthy eating habits usually maintain an adequate calcium balance and are as effective as pharmacological agents.

In contrast to calcium, vitamin D may be insufficient in otherwise adequate diets. In a meta-analysis of trials with a dose of more than 700 IU/day the pooled relative risk was 0.80 (95% CI 0.72–0.89, 33 265 subjects, 9 trials) for non-vertebral fractures and 0.82 (95% CI 0.69–0.97, 31 872 subjects, 5 trials) for hip fractures. Non-vertebral fracture rates were reduced in both community (29% fewer) and institutional (15% fewer) settings and the vitamin D effect was independent of calcium supplementation (Bischoff-Ferrari *et al.*, 2005).

The relationship between other dietary factors and osteoporosis is still unresolved. Soy-rich foods, natural progesterone, carbonated drinks, caffeine-containing beverages have not been tested rigorously enough to allow for firm clinical conclusions.

Smoking and alcohol

Smoking and excessive alcohol reflect an unhealthy lifestyle and as such are associated with an increased fracture risk. A direct effect, however, especially for alcohol intake, remains to be established. The BMD in post-menopausal smokers is 2% lower than average with each decade passed since the menopause. Stopping smoking decreases the risk of fractures, although a significant decrease is only noted 10 years after cessation.

Management of osteoporosis

The aim of any intervention in osteoporosis is the prevention of fractures in patients who have not yet fractured or prevention of disease progression in patients who have already sustained a fragility fracture. Management of osteoporotic patients involves general measures, non-pharmacological interventions and pharmacological interventions.

General measures include correction of deficiencies/insufficiencies in vitamin D (Bischoff-Ferrari *et al.*, 2005; Boonen *et al.*, 2007), and ensuring a calcium intake of about 1200 mg per day and a protein intake of 1.2 g/kg body weight (Kanis *et al.*, 2008a). This should be the first step in the management of a patient with osteoporosis. Non-pharmacological interventions mainly aim at reducing the frequency or impact of falls for example, with the use of hip protectors in residents of nursing homes at high risk for falling. Although fall prevention programs have been shown to reduce the number of falls (Neyens *et al.*, 2009), multifactorial fall prevention programs in primary care, community or emergency care settings have not been consistently effective in reducing the number of fallers or fall-related injuries (Gates *et al.*, 2008).

Pharmacological interventions aim at correcting the imbalance between bone resorption and bone formation by either inhibiting bone resorption or stimulating bone formation. Most available interventions are inhibitors of bone resorption and turnover. They include bisphosphonates, calcitonin, estrogens, SERMs. RCTs show that treatment improves BMD and reduces relative risk of fracture by about 50% for vertebral, 20–25% for non-vertebral and 40% for hip fractures (Cauley *et al.*, 2003; Black *et al.*, 2007; Wells *et al.*, 2008a, b; Cranney *et al.*, 2009; Eastell *et al.*, 2009), tibolone and denosumab (Cummings *et al.*, 2008, 2009). Owing to the low frequency of the event the reduction of absolute risk is much lower and varies depending on the baseline risk of studied patients e.g. between 1.7 and 11.1% for vertebral fractures with bisphosphonate treatment (MacLean *et al.*, 2008). In general, all available interventions reduce the risk of vertebral fractures which is a prerequisite for their regulatory approval. However, not all of them reduce the risk of non-vertebral fractures and only alendronate, risedronate, zoledronate, estrogens and denosumab have been shown to reduce the risk of hip fractures (Table IV). The only available stimulators of bone formation are PTH peptides, such as PTH 1–34 and PTH 1–84 that prevent vertebral, for both, and non-vertebral fractures for the former (MacLean *et al.*, 2008). Finally, there are also compounds whose action on bone remodeling has not yet been fully elucidated, such as strontium ranelate (O'Donnell *et al.*, 2006; Seeman *et al.*, 2006b). Strontium ranelate was effective in three trials among women with existing fractures, with a 37% reduction in vertebral fractures and a 14% reduction in non-vertebral fractures (O'Donnell *et al.*, 2006). In a separate analysis of women aged 80 years or more there were reductions in vertebral and non-vertebral fractures after treatment with strontium ranelate for 3 years (Seeman *et al.* 2006b). The frequency and route of administration vary widely depending on the specific pharmacological properties of each compound. Their efficacy is also highly dependent on adherence, which may be low with antiosteoporosis treatments.

There have been no head-to-head trials with fractures outcomes. In addition, fracture risk differs widely among patients included in different clinical trials precluding comparisons of the relative efficacies of

Table IV Protective effect of major pharmacological interventions on fracture risk in post-menopausal women with osteoporosis (Compston *et al.*, 2009).

	Vertebral fracture	Non-vertebral fracture	Hip fracture
HT*	+	+	+
Raloxifene	+	–	–
Alendronate	+	+	+
Ibandronate	+	–	–
Risedronate	+	+	+
Zoledronate	+	+	+
Strontium ranelate	+	+	–
Teriparatide	+	+	–
PTH (1-84)	+	–	–

+, evidence from RCTs and/or meta-analyses.

–, no evidence from existing RCTs or efficacy only demonstrated on *post hoc* subgroup analysis.

*, in women not selected on the base of osteoporosis or prevalent fracture.

different agents. For treatment decisions, apart from efficacy, other factors need to be carefully considered. These include the safety and tolerability of each individual agent, the convenience of administration and patient preferences for ensuring long-term adherence and the cost of the intervention. The hormone therapy with estrogen–progestogen increase rates of thromboembolism and estrogen and tibolone increase stroke rates (Rossouw *et al.*, 2007; Cummings *et al.*, 2008; MacLean *et al.*, 2008). The most common adverse events with bisphosphonates are upper gastrointestinal complaints (Solomon *et al.*, 2009). Oesophageal cancer is rare (1 in 20 000) but adverse event reporting has identified 23 cases associated with use of alendronate and other bisphosphonates (Wysocki, 2009). Osteonecrosis of the jaw (<1 per 100 000) also has been associated with bisphosphonate use in observational studies (Solomon *et al.*, 2009). Such a low incidence is found in bisphosphonate treatment for osteoporosis. It may be far higher in the treatment of bone metastases (Rizzoli *et al.*, 2008). In the denosumab trial, flatulence and eczema were more common, but serious adverse events were not more common with denosumab compared with placebo (Cummings *et al.*, 2009).

PTH use is associated with an increased incidence of nausea and headache (Neer *et al.*, 2001) while dizziness, nausea and leg cramps are more reported by teriparatide users (Body *et al.*, 2002).

Why treatment of osteoporosis does not guarantee fracture protection

In 1994 the WHO defined osteoporosis as BMD below a *T*-score of -2.5 SD and osteopenia as a *t*-score in the range of -1 SD to -2.5 SD. Osteopenia is not a disease in its own right but the term usefully describes the proportion of the population having bone loss that is not so severe as in those with osteoporosis. Osteoporosis is of clinical

importance primarily because it is associated with low-trauma fractures; the clinical emphasis is on fracture and fracture risk rather than BMD.

Because drug licensing regulatory requirements require fracture as the key clinical outcome of osteoporosis trials, many large clinical trials with fracture outcomes have been reported. In these trials, some bone active agents which have prevented bone loss have not reduced fractures at all relevant sites. Thus the hope that treatment of osteoporosis or osteopenia might guarantee protection from fracture is not realistic.

Osteopenia

Although osteoporosis is the more severe condition of reduced BMD it is still relevant to consider the milder state, osteopenia, for two reasons. First, even though the risk of fracture will be lower in people with osteopenia than osteoporosis, the osteopenia segment of the population is much larger than the osteoporosis segment. Thus, although their average fracture risk is lower than with osteoporosis, those with osteopenia make a greater contribution to the total number of fractures. Second, the fracture risk associated with a particular level of reduced BMD rises with age, so that an older woman with osteopenia may have a higher absolute risk of fracture than a younger woman with osteoporosis (Fig. 5) (Kanis *et al.*, 2002). The issues to address in the prevention of fracture include not only the efficacy of therapies, but also the multiple risk factors for fracture (risk of falling and bone strength), the persistence of therapeutic effect, the need for intervention thresholds and the need for a realistic health care policy framework in which the therapeutic strategy might be applied.

Role of risk factors

The four most important risk factors for bone fractures are female sex, older age, lower BMD and the existence of a previous low-trauma fracture. Other risk factors, independent of their effect on BMD, include a family history of hip fracture, rheumatoid arthritis, systemic glucocorticoid use, excessive alcohol intake and untreated premature menopause. The synthesis of these analyses has now been published by WHO (Kanis *et al.*, 2007). For females, for any given BMD, fracture risk increases steeply with each decade of age beyond 50 years (Fig. 5). The risk is further modulated by the presence of one of more independent risk factors. These have been synthesized in the algorithm underlying the web-based FRAX instrument for individualized fracture risk assessment (www.shef.ac.uk/FRAX). Authors using FRAX™ report that the use of the model compared with BMD alone may improve identification of patients at increased fracture risk (Lippuner *et al.*, 2010; Nanes and Kallen, 2009). Thus although BMD defines osteopenia and osteoporosis, additional risk factors are needed for a more accurate prediction of fracture risk.

Prevention failures

Nearly all of the treatments for osteoporosis act by reducing bone turnover rates and the improved bone density should lower fracture risk. Since bone strength is just one factor, however, fractures can still occur even in treated women if the sample is sufficiently large and observed over a sufficiently long period.

A useful example is the WHI study which involved more than 16 000 women age 50–79 years followed for more than 5 years after random allocation to combined estrogen/progestogen (E + P HT) or placebo. Unlike most osteoporosis studies the WHI population was not selected for low BMD and may be generally representative of the post-menopausal population. The study showed that around 5 years of effective therapy reduced but did not abolish fractures (Cauley *et al.*, 2003) and the results with other agents such as the bisphosphonates are similar.

Duration of effects

Although osteoporosis is a lifelong disease, most trials of effectiveness lasted <5 years and few guidelines advocate treatment for longer than 5 years. In an extension of one 3 year trial, bone density continued to increase with 10 mg of alendronate daily for up to 10 years (Bone *et al.*, 2004).

The duration of benefit after stopping therapy remains a matter of ongoing debate. Women who had taken alendronate for 5 years in a previous trial were randomly allocated to continue or discontinue for a further 5 years and non-vertebral fractures occurred in 19% of those continuing and 18% of those who discontinued alendronate (Black *et al.*, 2006). With respect to HT, it has been controversial whether the fracture reduction effect remains after discontinuation (Bagger *et al.*, 2004; Banks *et al.*, 2004; Yates *et al.*, 2004). In the WHI study, the significant hip fracture reduction during the trial was lost during the 3 years after the trial (Heiss *et al.*, 2008).

Cost-effectiveness

Cost-effectiveness modeling can influence whether treatment is restricted to those with osteoporosis or extended to those who have osteopenia. On the basis of cost-effectiveness, the UK National Institute for Healthcare and Clinical Excellence (NICE) Technology Appraisal on the Prevention of Fractures does not include women with osteopenia or younger women unless they have had a low-trauma fracture (NICE Technology appraisal, 2008a, b). In contrast, the National Osteoporosis Guideline Group (NOGG) (2008) takes age into account and includes the oldest women with osteopenia because their absolute fracture risk exceeds that of younger women with osteoporosis (Compston *et al.*, 2009).

In conclusion, treatment recommendations are no longer based primarily on BMD. As a result, those women with osteopenia who have relatively high fracture risk because of additional factors such as age, are also eligible for treatment. Although the large treatment trials demonstrate clear reduction of fracture risk, none of the treatment options can guarantee fracture prevention.

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Appendix

A meeting was organized by ESHRE (30–31 August 2009) to discuss the above subjects. The contributors included: David H. Barlow (Executive Dean of Medicine, Professor of Reproductive Medicine

University of Glasgow, UK), Philippe Bouchard (Hospital St Antoine APHP, Endocrinology Unit, Paris, France), Maria Luisa Brandi (Department of Internal Medicine, University of Florence, Italy), J.L.H. Evers (Dept. Obstet. Gynecol., Academic Hospital Maastricht, The Netherlands), A. Glasier (Family Planning and WW Services, Edinburgh, UK), Eva Negri (Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy), Socrates E. Papapoulos (Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands), Stuart H. Ralston (Head of the School of Molecular and Clinical Medicine and ARC Professor of Rheumatology Molecular Medicine Centre, Western General Hospital, Edinburgh, UK), René Rizzoli (Division of Bone Diseases, Department of Rehabilitation and Geriatrics, Faculty of Medicine, Geneva, Switzerland). The discussants included: D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), J. Collins (McMaster University, Hamilton, Canada), G. Benagiano (Dipartimento di Scienze Ginecologiche, Università di Roma, Italy), P.G. Crosignani (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy), C. La Vecchia (Istituto Mario Negri, Milano, Italy) and A. Volpe (Dipartimento Integrato Materno Infantile, Università di Modena, Italy). The report was prepared by J. Collins and P.G. Crosignani.