

PREVENTION AND MANAGEMENT OF OSTEOPOROSIS

Report of a
WHO Scientific Group



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PREVENTION AND MANAGEMENT OF OSTEOPOROSIS

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WHO Scientific Group Meeting on Prevention and Management of Osteoporosis

Geneva, 7–10 April 2000

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Abbreviations

The following abbreviations are used in this report:

AR	average requirement
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BMU	bone multicellular unit
BRU	bone remodelling unit
BSU	bone structural unit
CI	confidence interval
CT	computed tomography
CTX	C-terminal crosslink
DALY	disability-adjusted life year
DXA	dual-energy X-ray absorptiometry
EPIDOS	Epidemiologie de l'Ostéoporose [epidemiology of osteoporosis]
EVOS	European Vertebral Osteoporosis Study
FAVOS	Fluoride and Vertebral Osteoporosis Study
FIT	Fracture Intervention Trial
FOSIT	Fosamax International Study
GDP	gross domestic product
HDL	high-density lipoprotein
HRT	hormone replacement therapy
IGF	insulin-like growth factor
LDL	low-density lipoprotein
LTL	lowest threshold limit
MEDOS	Mediterranean Osteoporosis Study
MRI	magnetic resonance imaging
NHANES	National Health and Nutrition Examination Study
NIDDM	non-insulin-dependent diabetes mellitus
NNT	number needed to treat
PPV	positive predictive value
pQCT	QCT at peripheral sites
PRI	population reference intake
QALY	quality-adjusted life year
QCT	quantitative computed tomography
QUS	quantitative ultrasound
RR	relative risk
SD	standard deviation
SERM	selective estrogen receptor modulator
SOF	Study of Osteoporotic Fractures

SOS	speed of sound
TNF	tumour necrosis factor
TSH	thyroid-stimulating hormone

1. Introduction

A WHO Scientific Group on Prevention and Management of Osteoporosis met in Geneva from 7 to 10 April 2000. The meeting was opened by Dr N. Khaltaev, Responsible Officer for Chronic Respiratory Diseases and Arthritis, who welcomed the participants on behalf of the Director-General of the World Health Organization.

1.1 Background

Osteoporosis is an established and well-defined disease that affects more than 75 million people in Europe, Japan and the USA, and causes more than 2.3 million fractures annually in Europe and the USA alone. The lifetime risk for hip, vertebral and forearm (wrist) fractures has been estimated to be approximately 40%, similar to that for coronary heart disease. Osteoporosis does not only cause fractures, it also causes people to become bedridden with secondary complications that may be life threatening in the elderly. Since osteoporosis also causes back pain and loss of height, prevention of the disease and its associated fractures is essential for maintaining health, quality of life, and independence among the elderly. In May 1998, the Fifty-first World Health Assembly, having considered *The World Health Report 1997* (1), which described the high rates of mortality, morbidity and disability from major noncommunicable diseases, including osteoporosis, requested the Director-General to formulate a global strategy for prevention and control of noncommunicable diseases (2). In direct response to this resolution, WHO established a task force to develop a strategy for the management and prevention of osteoporosis. The resulting project is aimed at improving the diagnosis and care of osteoporosis patients worldwide, but especially those in developing countries.

The first step of the project was the meeting of the WHO Scientific Group on the Prevention and Management of Osteoporosis, which resulted in the development of this report. An interim version of this report was published in 1999 (3). This final report has been reviewed by the major academic, governmental and nongovernmental organizations concerned with osteoporosis and approved by WHO.

This report will be used as a basis for the preparation of a series of practical guides for the management of osteoporosis aimed at primary care physicians throughout the world. Educational materials will also be developed for use in conjunction with the guides, and are expected to have a major impact on osteoporosis management throughout the world.

1.2 Definition of the problem

Osteoporosis is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility (4). Early osteoporosis is not usually diagnosed and remains asymptomatic; it does not become clinically evident until fractures occur. Loss of bone density occurs with advancing age and rates of fracture increase markedly with age, giving rise to significant morbidity and some mortality (5).

Osteoporosis is three times more common in women than in men, partly because women have a lower peak bone mass and partly because of the hormonal changes that occur at the menopause. Estrogens have an important function in preserving bone mass during adulthood, and bone loss occurs as levels decline, usually from around the age of 50 years. In addition, women live longer than men (6) and therefore have greater reductions in bone mass.

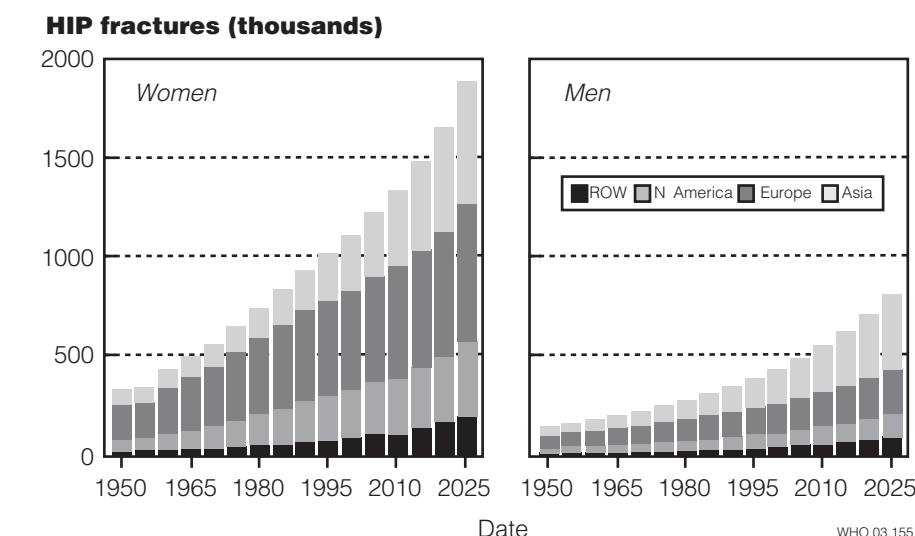
Increasing life expectancy in many parts of the world means that women now live more than one-third of their lives after the menopause, and that the number of postmenopausal women is increasing. In Europe, for example, the number of women over 50 years of age is projected to increase by 30%–40% between 1990 and 2025 (6). Among men over 50 years, the projected increase is expected to be even higher (50%). This trend is even more marked in other areas of the world. In North America, the proportion of the population over 50 years is expected nearly to double. The proportionate increases will be greatest in Africa, Asia and Latin America, but Asia will have the highest absolute increase because it has the largest population.

An estimated 1.3–1.7 million hip fractures occurred worldwide in 1990 (7, 8). By 2025, this number is expected to increase to almost 3 million (Figure 1). This is probably an underestimate, since in many regions, hip fracture rates have increased even after age has been taken into consideration (8) (see section 2.4). These projected estimates are relatively robust, since the group they apply to has already been born.

1.3 The burden of disease

In osteoporosis, the morbidity of the disease arises from the associated fractures. The pathogenesis of fractures depends on many factors other than osteoporosis. For example, extraskeletal factors, such as the risk of falling, increase with age and contribute to the risk of fracture (see section 2.5). However, fractures associated with osteoporosis have a clear pattern. The most common fractures are those of the hip, vertebrae and forearm. In addition, many fractures at other

Figure 1
Estimates of the number of hip fractures between 1950 and 2025 by gender and region^a



ROW: rest of the world.
^a Modified from reference 8.

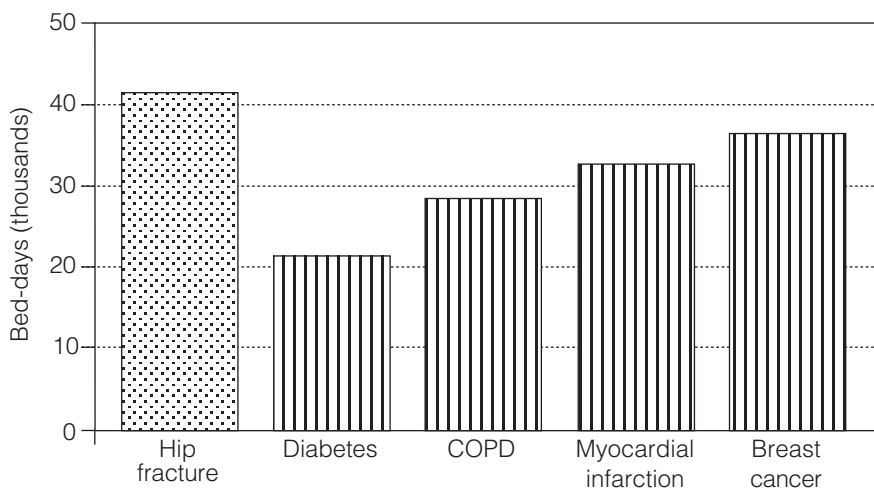
sites are also associated with low bone density independently of age, and are at least partly due to osteoporosis (9). Although fractures due to osteoporosis usually heal normally, they are attended by an increased risk of serious functional impairment and institutionalization (10).

1.3.1 Hip fracture

The most serious osteoporotic fracture is that of the hip. Hip fractures typically result from falls, but some occur spontaneously. Women are more often affected than men and the incidence rates rise exponentially with age. The lifetime risk of hip fracture lies between 14% and 20% among Caucasian women in Europe and the USA, and is likely to increase as mortality for other conditions declines (11). In most countries rates among men are substantially lower (12–14). In those countries where the risk in women is very low, the sex ratio is much smaller. Indeed, in several regions the risk is higher in men than in women (13).

Hip fractures are usually painful, and nearly always necessitate hospitalization. In many countries, the mean hospital stay is 30 days. The

Figure 2
Hospital bed-days for hip fracture and other chronic diseases in women aged 45 years or more from the Trent Region of the United Kingdom^a



WHO 03.156

^a Adapted from reference 15 with permission from Springer-Verlag and the authors.

number of hospital bed-days accounted for by hip fracture among women is similar to that for cardiovascular disease, breast cancer and chronic obstructive pulmonary disease (15) (Figure 2).

Most hip fractures heal, but with a high degree of morbidity and appreciable mortality, depending in part on the patient’s age, the treatment given and associated morbidity (16). Furthermore, immobility increases the risk of complications. The prognosis is much poorer where surgery is delayed for more than 3 days. Up to 20% of patients die in the first year following hip fracture, mostly as a result of a preexisting medical condition (17), and only about one-third of survivors regain their original level of function (10). In the USA, approximately 20% of hip fracture patients require long-term care in a nursing home (18). Similar rates are reported for many other countries.

Persons already in poor health may suffer more hip fractures than the general community, and the greater coexisting morbidity in patients with hip fracture than in those without hip fracture supports this view. The implications of this comorbidity for the cost and benefits of interventions are important to consider since treatment may not avoid all deaths associated with hip fracture.

1.3.2 **Vertebral fracture**

Identifying the incidence of vertebral fractures and their attendant morbidity may be difficult because many are asymptomatic or cause too few symptoms to provoke investigation (19, 20). Available data indicate that the incidence of vertebral fractures, like that of other osteoporotic fractures, is greater among women than among men and increases with age. Between the ages of 60 and 90 years, the incidence rises 20-fold in women but only 10-fold in men (21). This age-related increase is less than that observed for hip fractures and there is also less variation in incidence rates among countries than for hip fractures (22).

Vertebral fractures that come to clinical attention cause a significant decrease in the quality of life, although the impact is less than that of hip fractures. Approximately 4% of women with a vertebral fracture need assistance in conducting activities of daily living (10). Quality of life becomes progressively impaired as the number and severity of vertebral fractures increases (23).

Vertebral fracture rarely leads to hospitalization; in the United Kingdom, as few as 2% of patients may be admitted, although this figure may be an underestimate depending on the accuracy of coding clinical cases (21). The economic burden is mainly due to outpatient care, provision of nursing care and lost working days. Most of these costs are confined to those with severe or multiple vertebral deformities (24). As shown in Table 1, however, the adverse influence of vertebral fractures on many of the activities of daily living is almost as great as that seen for hip fractures (25). In contrast to hip fractures, vertebral fractures do not increase the risk of premature mortality. Instead, survival appears to worsen with the passage of time, probably as the result of underlying diseases that increase the risk both of vertebral fracture and of death (26).

1.3.3 **Forearm fracture**

Fractures of the distal forearm are common among the middle-aged and elderly and are generally caused by a fall on the outstretched hand (5). The incidence in women typically increases markedly within 5 years of the menopause, reaches a peak between the ages of 60 and 70 years and levels off thereafter. Age-related increases in fracture rates are much less marked among men.

Although fractures of the wrist cause less morbidity than hip fractures (see Table 1), are rarely fatal and seldom require hospitalization, the consequences are often underestimated. Forearm fractures are painful, and usually require one or more surgical or manipulative

Table 1
Physical and functional impairment associated with selected minimal trauma fractures among women in Rancho Bernardo, CA, USA

Physical or functional impairment	Odds of impairment (95% CI) ^a		
	Hip fracture	Spine fracture	Wrist fracture
<i>Movements</i>			
Bend	2.73 (1.09–6.84)	3.06 (1.20–7.80)	1.23 (0.61–2.48)
Lift	1.11 (0.34–3.62)	3.42 (1.23–9.50)	1.26 (0.62–2.56)
Reach	1.46 (0.48–4.48)	0.69 (0.17–3.06)	1.78 (0.86–3.67)
Walk	3.57 (1.42–8.95)	2.66 (0.96–7.39)	1.61 (0.77–3.40)
Climb stairs	2.57 (0.95–6.96)	2.23 (0.74–6.70)	1.81 (0.90–3.65)
Descend stairs	4.12 (1.53–11.11)	4.21 (1.52–11.64)	2.54 (1.21–5.34)
Get into/out of car	1.33 (0.50–3.50)	2.13 (0.80–5.62)	1.26 (0.64–2.47)
<i>Activities</i>			
Put socks on	1.63 (0.61–4.36)	1.66 (0.60–4.64)	1.08 (0.53–2.22)
Cook meals	11.14 (2.40–51.72)	6.93 (1.55–30.99)	10.19 (3.25–31.90)
Shop	4.60 (1.35–15.70)	5.20 (1.61–16.78)	3.26 (1.34–7.96)
Heavy housework	2.81 (1.00–7.87)	2.10 (0.79–5.58)	1.60 (0.88–2.91)

CI, confidence interval.
^a Likelihood of having the impaired movement or activity following fracture after adjusting for age, body mass index, estrogen use, visual impairment and reduced mental status.
 Modified from reference 25.

procedures to reposition the bones, and 4–6 weeks of immobilization in plaster. Approximately 1% of patients with forearm fracture become dependent on others for activities of daily living as a result of the fracture (10), but nearly half report only fair or poor functional outcomes at 6 months (27). Algodystrophy is common, which gives rise to pain, tenderness, stiffness, swelling of the hand, and more rarely, frozen shoulder syndrome (28). Forearm fractures increase the risk of other osteoporotic fractures in later life (29), but do not increase mortality (26).

1.3.4 **Costs**

The total cost of osteoporosis is difficult to calculate because it includes the costs of acute hospital care, loss of working days for family carers, long-term care and medication. Cost estimates are based on many assumptions, making cost comparisons between countries difficult if not impossible. In addition, few direct international comparisons have been made utilizing the same instruments (see section 6.3).

The bulk of the cost of osteoporosis is attributable to hip fracture because of the need for hospitalization and subsequent home care or nursing home care. In the United States, hip fractures account for more than half of all osteoporosis-related admissions (5). In England

and Wales, hip fracture patients occupy one fifth of all orthopaedic beds and account for nearly 90% of the acute hospital costs of osteoporotic fractures (16). Similar figures have been derived from other European countries (30).

1.4 Possibilities for the future

Until recently, osteoporosis was an under-recognized disease and considered an inevitable consequence of ageing. However, perceptions have changed, as epidemiological studies have highlighted the high burden of the disease and its costs to society and health care systems. Improvements in diagnostic technology and assessment facilities over the past decade now mean that it is possible to detect the disease before fractures occur.

The cornerstone of diagnosis is the measurement of bone mineral density. Diagnostic thresholds offered by the World Health Organization have been widely accepted (31). These are optimally applied at the hip with dual energy X-ray absorptiometry. In addition, many other techniques and clinical risk factors for fractures have been identified and can be used to select patients for assessment and intervention (see section 4). Furthermore, the development and use of treatments of demonstrated efficacy have begun to reduce the burden of osteoporotic fractures (see section 5).

Against this background, WHO considers osteoporosis to be of increasing importance. The Director-General of the World Health Organization has stated (3), “WHO sees the need for a global strategy for prevention and control of osteoporosis focusing on three major functions: prevention, management and surveillance”. To amplify the existing and past activities of WHO in osteoporosis, this report provides a core resource for developing guidelines for clinical care, diagnosis and policy with the goal of enhancing the management of osteoporosis throughout the world.

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2. Pathogenesis of osteoporosis and related fractures

2.1 Normal characteristics of bone

2.1.1 *Morphology*

The bones of the adult skeleton comprise two types of tissue, cortical or compact, and cancellous or spongy bone. Most bones consist of an outer cortical sheath enclosing a trabecular network of cancellous bone that houses the marrow. The cortical sheath is bounded outside and inside by the periosteal and endosteal surfaces, respectively. The endosteal surface of the cortical sheath is connected to cancellous bone and consists of interconnected rods and plates. This structure maximizes strength while minimizing weight. The rods and plates of the cancellous network are preferentially oriented along the lines of mechanical strain of the bone.

In adults, 80% of the skeleton is cortical bone. However, the relative proportions of cortical and cancellous bone vary in different parts of the skeleton. For instance, in the lumbar spine, cancellous bone accounts for about 70% of the total bone tissue, whereas in the femoral neck and radial diaphysis, it accounts for about 50% and 5%, respectively (1–3).

2.1.2 *Composition of bone*

Bone mineral

The mineral component of bone accounts for about 65% of its total dry weight. Chemically, it is predominantly hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. Other constituents, such as carbonates, citrate, magnesium, sodium, fluoride and strontium, are either incorporated into the hydroxyapatite crystal lattice or adsorbed on to the surface. Some substances, e.g. bisphosphonates, have a special affinity for bone mineral (1–3).

Bone organic matrix

The organic matrix accounts for approximately 35% of the total dry weight of bone. Approximately 90% of this matrix consists of bone-specific collagen; the remainder consists of non-collagenous proteins, such as osteonectin, osteocalcin (formerly referred to as bone Gla protein), osteopontin and bone sialoprotein. The matrix proteins are synthesized and laid down by osteoblasts. Collagen fibres are usually oriented in a preferential direction, giving rise to a typical lamellar structure. The lamellae are generally parallel to each other if deposited along a flat surface such as the surface of the trabecular network or the periosteum, or concentric if synthesized within cortical

bone on a surface that borders a channel centered on a blood vessel. These concentric structures within cortical bone are known as osteons or haversian systems (4, 5). The plasma concentration and/or the urinary excretion of collagen products and certain non-collagenous proteins such as osteocalcin reflect the rate of bone formation and resorption (6) and are used clinically as biochemical markers of bone turnover (see section 4.4.3).

Bone cells

Osteoblasts are bone-forming cells. They originate from local mesenchymal stem cells (bone marrow stroma or connective tissue mesenchyme), which undergo proliferation and differentiate to preosteoblasts and then to mature osteoblasts (7). The osteoblasts form a unidirectional epithelial-like structure at the surface of the organic matrix. The thickness of this layer, called osteoid, depends on the time between matrix formation and its subsequent calcification — termed primary mineralization. Transport systems located in the plasma membrane of osteoblasts are responsible for the transfer of bone mineral ions, mainly calcium and phosphate, from the extracellular space of the bone marrow to the osteoid layer (8). The plasma membrane of osteoblasts is rich in alkaline phosphatase, which enters the systemic circulation. The plasma concentration of this enzyme is used as a biochemical marker of bone formation. Towards the end of the production of the bone matrix and the deposition of mineral ions, the osteoblasts become either flat lining cells or osteocytes (9). A slow process of mineral deposition (secondary mineralization) completes the process of bone formation (10).

Osteocytes originate from osteoblasts embedded in the organic bone matrix, which subsequently become mineralized. They have numerous long cell processes forming a network of thin canaliculi that connects them with active osteoblasts and flat lining cells. Fluid from the extracellular space in the bone marrow circulates in this network. Osteocytes probably play a role in the homeostasis of this extracellular fluid and in the local activation of bone formation and/or resorption in response to mechanical loads (9).

Osteoclasts are giant cells containing 4–20 nuclei that resorb bone. They originate from haematopoietic stem cells, probably of the mononuclear/phagocytic lineage (11), and are found in contact with the calcified bone surface within cavities called Howship's lacunae (also known as resorptive lacunae) that result from their resorptive activity. Osteoclastic resorption takes place at the cell/bone interface in a sealed-off microenvironment (12, 13). In this regard, the most prominent ultrastructural feature of osteoclasts is the deep folding of

the plasma membrane, called the ruffled border, in the area apposed to the bone matrix. This structure is surrounded by a peripheral ring tightly adherent to the bone matrix, which seals off the sub-osteoclastic resorbing compartment.

The mechanism of bone resorption involves the secretion of hydrogen ions and proteolytic enzymes into the sub-osteoclastic resorbing compartment. The hydrogen ions dissolve the bone minerals, thereby exposing the organic matrix to the proteolytic enzymes (12, 13). These enzymes, which include collagenases and cathepsins, are responsible for the breakdown of the organic matrix. The process releases the minerals that contribute to calcium and phosphate homeostasis. Accordingly, biochemical markers of collagen degradation, such as hydroxyproline and pyridinoline crosslinks, which are found in plasma and urine, can provide estimates of the bone resorption rate (5, 6).

2.1.3 **Physiology**

Both the shape and structure of bone are continuously renovated and modified by the processes of modelling and remodelling.

Bone modelling

Bone modelling begins with the development of the skeleton during fetal life and continues until the end of the second decade, when the longitudinal growth of the skeleton is completed. In the modelling process, bone is formed at locations that differ from the sites of resorption, leading to a change in the shape or macroarchitecture of the skeleton. Longitudinal growth of a typical long bone, such as the tibia, depends on the proliferation and differentiation of cartilage cells in the epiphyseal (growth) plate. Cross-sectional growth, such as the increase in girth of the radial diaphysis, occurs as new bone is laid down beneath the periosteum. Simultaneously bone is resorbed at the endosteal surface.

Bone modelling may continue, but to a lesser extent, during adult life when resorption at the end endosteal surface increases the mechanical strain on the remaining cortical bone, leading to the stimulation of periosteal bone apposition. This phenomenon, which increases with ageing and is somewhat more pronounced in men than in women, offsets in part the negative effects of bone resorption at the endosteal surface on mechanical strength (1–3).

Bone remodelling

Bone remodelling occurs simultaneously with modelling from fetal life through to skeletal maturity, when it becomes the predominant

process that occurs throughout adult life. Remodelling maintains the mechanical integrity of the skeleton by replacing old bone with new. Bone resorption and bone formation occur at the same place, so that there is no change in the shape of the bone. This constant process of turnover enables the skeleton to release calcium phosphate whenever the net intestinal absorption of this mineral is less than the amount excreted in urine (14).

In the adult skeleton, approximately 5–10% of the existing bone is replaced every year through remodelling. This does not occur uniformly throughout the skeleton, but in focal or discrete sites. The morphological dynamic structure of turnover is the “basic multicellular unit” (BMU), also called the “bone remodelling unit” (BRU). The morphological entity formed when the process is terminated is called the “bone structural unit” (BSU) (15). The BSU corresponds to a “packet” in cancellous bone, and to an osteon in cortical bone.

In both cortical and cancellous bone, the remodelling process begins with bone resorption by osteoclasts. This phase is over within a few days and is followed by the departure of multinucleated osteoclasts and the reversal phase.

In the reversal phase, mononuclear cells line the resorption lacunae and deposit a cement line marking the limit of prior erosion and the newly formed bone. These mononuclear cells are subsequently replaced by osteoprogenitor cells, which differentiate into cuboidal-shaped osteoblasts. Organic matrix is then laid down, followed by the deposition of minerals. The lacunae are gradually filled with new bone over several months. Thereafter, the osteoblasts change shape and eventually become flattened lining cells, and the osteoid seam narrows and eventually disappears. This process of bone resorption followed by formation at the same locus is termed “coupling” (16–18).

The remodelling process is controlled by systemic and locally produced cytokines (16–19). The maintenance of a normal, healthy, mechanically competent skeletal mass depends on keeping the process of bone resorption and formation in balance. Failure to match bone formation with bone resorption results in net bone loss. This is what occurs in osteoporosis, whether as a result of deficiency of sex hormone, primary hyperparathyroidism, hyperthyroidism or endogenous or exogenous exposure to excess glucocorticoids.

Communication between osteoblasts and osteoclasts

Osteoclast formation is controlled by several circulating hormones, including parathyroid hormone $1\alpha,25$ -dihydroxycholecalciferol

(calcitriol), and the gonadal steroids, estrogen and testosterone (18). The microenvironment of the bone marrow also plays an essential role as a source of cytokines such as tumour necrosis factors (TNFs) and interleukins (20, 21), which also regulate osteoclast formation and activity. These systemic and local factors regulate osteoclast formation and activity.

Hormones and cytokines act on the osteoblastic lineage cells, which possess a cell surface molecule known as RANK ligand (RANKL, formerly known as osteoclast differentiation factor, TRANCE), and a cell surface receptor, osteoprotegerin (22). RANKL is a member of the TNF ligand family that is present in osteoblastic lineage cells and interacts with osteoclast precursors from the haematopoietic lineage. This interaction promotes the differentiation and fusion of the osteoclast precursor, thus leading to the formation of mature osteoclasts. Osteoprotegerin is a soluble member of the TNF receptor superfamily that is produced by osteoblast lineage cells and inhibits osteoclast formation (22).

Mechanisms of hormone action. Calcitonin inhibits bone resorption by acting directly on mature osteoclasts (23). Bisphosphonates, which are used in treating osteoporosis, also inhibit osteoclasts, probably by interfering with the system of communication between osteoblasts and osteoclasts (3). They also reduce the number of osteoclasts by inhibiting either their recruitment or their survival. Estrogen and probably testosterone exert their effects on the bone resorption by inhibiting the production of cytokines, particularly TNFs, interleukin-1 and interleukin-6 (20, 21, 24, 25).

Growth factors. Osteoblast formation requires a transcription factor named *cbfal osf2*, which controls osteoblast differentiation and bone formation in the developing skeletons as well as the function of mature differentiated osteoblasts (26, 27). Several growth factors, including insulin-like growth factors (IGFs), transforming growth factor- β , fibroblast growth factors, platelet-derived growth factor, bone morphogenetic proteins and prostaglandins can stimulate the proliferation of osteoblasts in vitro (28). Their respective importance in vivo is not yet clear. Nevertheless, it has been suggested that the production and action of growth factors are vital to the stimulation of bone formation in response to systemic hormones such as parathyroid hormone (PTH), osteogenic agents such as fluoride, and mechanical strain (17).

2.1.4 **Calcium homeostasis**

Virtually all (99%) of the body's calcium is located in bone and teeth. Only 0.1% is in the extracellular compartment and the remainder is within cells. The maintenance of a constant extracellular concentration of ionized calcium is essential, because calcium influences many physiological functions and biochemical pathways.

The extracellular concentration of calcium is regulated by a dynamic equilibrium between the levels calcium in the intestine, kidney and bone (14). In young adults, the rates of calcium entering and leaving the extracellular compartment are equal. Net intestinal absorption of calcium corresponds to the difference between the amount of calcium absorbed and that diffusing from the extracellular compartment to the intestinal lumen. The urinary excretion of calcium represents the difference between the amount filtered and that reabsorbed. In a steady state, urinary calcium excretion corresponds roughly to the net calcium fluxes entering the extracellular compartment from the intestine and bone. In the kidney 98% of the calcium filtered by the glomerulus is reabsorbed in the renal tubule.

The major regulator of the intestinal absorption of calcium is calcitriol, an active metabolite of vitamin D₃ (29, 30), which acts as a hormone. It is formed in the kidney, and its production is controlled by PTH, IGF-1, and the extracellular concentrations of calcium and phosphate (30, 31).

The main regulator of the tubular reabsorption of calcium is PTH (32), secretion of which is controlled by the extracellular concentration of calcium (32).

2.2 **Gain of bone**

2.2.1 **Peak bone mass**

The “peak bone mass” is the amount of bone tissue present at the end of skeletal maturation (33). It is a major determinant of the risk of fracture due to osteoporosis since the mass of bone tissue at any time during adult life is the difference between the amount accumulated at maturity and that lost with ageing. There is, therefore, considerable interest in exploring ways to increase peak bone mass. Epidemiological studies indicate a 10% increase in peak bone mass in the Caucasian female population would decrease the risk of hip fracture by about 30% (34). Such an increase would roughly correspond to the difference between male and female peak bone mass as measured at the radial or femoral diaphyseal site.

2.2.2 *Measurement of bone mass*

Most information in the characteristics of skeletal growth during childhood and adolescence has been obtained by non-invasive techniques that enable bone mass to be measured at various sites in the skeleton with great precision and accuracy. The bone mass of a particular part of the skeleton is directly dependent on both the volume or size of the part concerned and the density of the mineralized tissue contained within its periosteal envelope. The mean volumetric mineral density of bony tissue (in g of hydroxyapatite per cm³) can be determined non-invasively by quantitative computed tomography (QCT) (35). The so-called “areal” or “surface” bone mineral density (BMD in g of hydroxyapatite per cm²) can be determined by single- or dual-energy X-ray absorptiometry (SXA and DXA). The values generated by these techniques are directly dependent on both the size and integrated mineral density of the scanned skeletal tissue. The integrated mineral density is determined by cortical thickness, the number and thickness of the trabeculae, and the “true” mineral density corresponding to the amount of hydroxyapatite per unit volume of the bone organic matrix.

Although the term BMD, without the additional “areal” qualification, is widely used, SXA and DXA do not measure the volumetric density. The BMD is the summation of several structural components which may evolve differently in response to genetic and environmental factors (36). Nevertheless, the term remains of clinical relevance in the assessment of gain or loss of bone mass (see sections 4.2–4.4), since BMD is directly proportional to bone strength, i.e. to the resistance of the skeleton to mechanical stress, both in vivo and in vitro.

2.2.3 *Development of bone mass*

There is no evidence for sex differences in bone mass of either the axial or appendicular skeleton at birth. Similarly, the volumetric BMD appears to be the same in female and male newborns. This absence of a substantial sex difference in bone mass is maintained until the onset of puberty (37). The difference following puberty is characterized by a more prolonged period of bone maturation in males than in females, resulting in a greater increase in bone size and cortical thickness. Puberty has a much greater effect on bone size than on the volumetric mineral density (37, 38). There is no significant sex difference in the volumetric trabecular density at the end of puberty. During puberty, the rate of accumulation of BMD at both the lumbar spine and femoral neck increases 4–6-fold over a 3- and 4-year period in females and males, respectively. The rate of increase in bone mass is less marked in the diaphysis of long bones than elsewhere. There is

an asynchrony between the gain in standing height and the growth of bone mineral mass during puberty (39). This phenomenon may be responsible for the transient fragility that may contribute to the higher incidence of fracture that occurs near puberty when the dissociation between the rate of statural growth and mineral mass accrual is maximal (40).

2.2.4 Attainment of peak bone mass

In adolescent girls, the gain in BMD declines rapidly after menarche and is insignificant 2 years later. In adolescent boys, the gain in BMD or in bone mineral content (BMC) is particularly rapid between the ages of 13 and 17 years but declines markedly thereafter in all sites except the lumbar spine and mid-femur, where growth continues until the age of 20 years. However, no significant increase in BMD is observed at the femoral neck. During late puberty, when height is increasing by less than 1 cm/year, the gain in bone mass is still significant in males but not in females (39). This suggests an important sex difference in the magnitude and/or duration of the so-called “consolidation” phase that contributes to the ultimate peak bone mass.

Studies using QCT also indicate that the peak volumetric mineral density of the lumbar spine is also achieved soon after menarche. No difference was observed between the mean values of subjects aged 16 and 30 years (41). This is consistent with many observations indicating that bone mass does not change significantly between the third and fifth decades. However, a few studies, mainly of a cross-sectional nature, suggest that bone mass may still be increasing during the third and fourth decades (37, 42). It has been suggested that environmental factors such as dietary calcium and/or physical activity might modify the time of attainment of peak bone mass.

Despite peak bone mass being essentially maximal at the end of puberty, radiogrammetry measurements of external diameter indicate that the external shape of many bones enlarges during adult life (43, 44). This may be secondary to increased bone resorption at the endosteal surface with enlargement of the internal diameter.

2.2.5 Variance in peak bone mass

At the beginning of the third decade, there is a large variability in the normal values of BMD in the axial and appendicular skeleton (33), particularly at sites susceptible to osteoporotic fractures, such as the lumbar spine and femoral neck. This variance is not substantially reduced by correction for standing height, and does not appear to increase significantly during adult life (39). It is already present before

puberty, and appears to increase still further during puberty at sites such as the lumbar spine and femoral neck. In young healthy adults, the variance in BMC of the lumbar spine is 4–5 times that of standing height (45). The variance in standing height does not increase during puberty (39).

2.2.6 **Determinants of peak bone mass**

Determinants of peak bone mass include heredity, sex, dietary factors, endocrine factors, mechanical forces and exposure to risk factors.

Heredity

Twin and family studies suggest that genetic or inherited factors may account for up to 50% or more of the variance in BMD and BMC values in the population (46, 47). Measurement of BMD at critical sites, such as the lumbar spine and femoral neck, as well as the distal forearm, indicates that monozygotic (identical) twins are much more similar to each other than dizygotic (non-identical) twins. This disparity between monozygotic and dizygotic twins is attributed to genetic factors, but differences in intrauterine nutrition may also contribute. The contribution of genetic factors to bone mineral mass and density is slightly less at the proximal femur and the forearm than at the lumbar spine, suggesting that the impact of genetic (or genetic and environmental factors) varies according to the skeletal site (46). Genetic determinants appear to be expressed before puberty as shown by correlation in BMD, BMC, bone size, and the estimated volumetric BMD between prepubertal daughters and their premenopausal mothers, a model in which half of the genes are common (48). During puberty, as for height, accrual of bone mineral mass follows a predictable track, as indicated by the close correlations that are formed between age-adjusted values of BMD recorded at yearly intervals in prepubertal girls (48).

The heritability of peak bone mass is likely to be polygenic. Several potential candidate genes have been explored in linkage and association studies (49). Some studies have indicated that polymorphisms of the vitamin D receptor gene are strongly related to bone mass, while others have reported that the relationship between genotype and phenotype is the opposite of that originally described (50). Polymorphisms in the promoter region of the *COL1a1* gene were recently reported to be significantly related to bone mass in the spine and to the presence or absence of vertebral fractures, but further studies are required. Other candidate genes include the estrogen and calcitonin receptor genes and genes for various cytokines and growth factors

such as transforming growth factor β 1 and interleukin-6. However, the functional significance of genotype differences has yet to be unequivocally demonstrated for any of these genes. The exact nature of the genetic determinant of peak bone mass is still not known. Because of the biological complexity of bone development, a large array of genes is probably involved in the determination of peak bone mass and strength at various skeletal sites.

Endocrine factors and calcium phosphate metabolism during growth

Various endocrine factors, including gonadal sex hormones and adrenal androgens (dehydroepiandrosterone and androstenedione) influence bone growth. The production of these steroids increases before and during puberty, but the time-course of their production does not match the accelerated gain in bone mass (37). In contrast, IGF-1 and calcitriol concentrations and the tubular reabsorption of inorganic phosphate and plasma phosphate rise with the accrual of bone mass. This may be an adaptive response to the increased demand for calcium and phosphate (37).

External factors

Modification of environmental factors can cause an individual to change the track of bone accrual. Nutritional factors are particularly important determinants of peak bone mass and rate of gain of bone mass. In addition to the non-specific influence of caloric intake, both experimental and clinical evidence indicate that the amount of calcium and protein in the diet modulate the gain in bone mass (see section 3.5.5). Several intervention studies report that calcium supplementation significantly enhances the rate of BMD in children and adolescents (see section 5.2.1). The role of physical activity is discussed later (see section 3.5.6).

Interactions between environmental factors such as dietary intake and physical exercise, as well as between genetic and environmental factors, might play an important role in the acquisition of bone mineral mass. Some data suggest that the magnitude of the bone response to calcium supplementation in prepubertal children varies according to the genotype of the vitamin D receptor (51, 52). However, prospective studies in groups of children randomized by genotype are required to establish whether such an interaction exists.

2.2.7 Disorders impairing peak bone mass

Various disorders impair the optimal acquisition of bone mass during childhood and adolescence (53). In certain disorders, such as Turner syndrome, Klinefelter syndrome, glucocorticoid excess,

hyperthyroidism or growth hormone deficiency, low peak bone mass has been attributed to abnormalities in a single hormone. In diseases such as anorexia nervosa and exercise-associated amenorrhoea, malnutrition, sex steroid deficiency and other factors combine to increase the risk of osteopenia or low bone mass (see below). This is probably also the case for various chronic diseases, which in addition may require therapies that affect bone metabolism.

Delayed puberty

Delayed puberty is defined as the absence of any sign of puberty at the attainment of the upper normal limit of chronological age for its onset (54); in boys, this means no increase in testicular volume at 14 years of age, and in girls, no breast development at 13 years of age. Epidemiological studies have provided indirect evidence that late menarche decreases peak bone mass and is a risk factor for osteoporosis. In addition, osteopenia has been reported in a cohort of men with a history of delayed puberty (55).

The causes of delayed puberty have been classified into permanent and temporary disorders (54). The permanent causes are due to failure of the hypothalamo-pituitary-gonadal axis (54). Among the temporary causes, many are due to chronic systemic diseases, nutritional disorders, psychological stress, intensive competitive training, or hormonal disturbances such as hyposecretion of thyroid hormones or growth hormone, or hypercortisolism (54). However, the most common cause of delayed puberty is the so-called “constitutional delay of growth and puberty”. It is a transient disorder with, in some cases, a familial history of late menarche of the mother or sisters, or a delayed growth spurt in the father. This condition has been considered as an extreme form of the physiological variation of the timing of the onset of puberty for which the “normal” range is about 8–12 and 9–13 years of age in girls and boys, respectively. The onset of puberty is a complex process involving the activation of the hypothalamic-pituitary-gonadal axis and other endocrine systems such as the growth hormone-IGF axis of which the targets include factors influencing the bone mineral balance and the growth rate of the skeleton. Several mechanisms have been suggested whereby constitutional delay of growth and puberty leads to a low peak bone mass (56).

Anorexia nervosa

Significant deficits in both cancellous and cortical bone are observed in young adult women with chronic anorexia nervosa, and may be severe enough to result in osteoporotic fractures. Several factors contribute to the reduced acquisition of bone mass in anorexia nervosa,

including low protein intake resulting in a reduction in IGF-1 production, and thereby decreased bone formation, low calcium intake enhancing bone resorption, estrogen deficiency, and glucocorticoid excess (53).

Exercise-associated amenorrhoea

The acquisition of bone mass may be impaired when women with hypogonadism and low body weight engage in intensive physical activity. As in anorexia nervosa, both nutritional and hormonal factors probably contribute. Intake of energy, protein and calcium may be inadequate, because athletes follow diets designed to maintain an optimal physique for their sport. Intensive training during childhood may contribute to the later onset and completion of puberty. Hypogonadism, as expressed by oligomenorrhoea or amenorrhoea, may give rise to bone loss in females who begin training intensively after menarche (53).

2.3 Loss of bone

The onset of substantial bone loss is usually around age 65 years in men and 50 years in women (57). Nevertheless, even in the absence of risk factors, some bone loss can be detected before the menopause at certain skeletal sites. Indeed, a decrease in BMD of the proximal femur has been described in the third decade. There is little variation in bone size throughout life, beyond continuous, slight expansion of the outer dimensions. This phenomenon is more marked in men than in women, and affects both the axial and the peripheral skeleton (43, 44). The expansion of the periosteal surface is less than the increase in space occupied by the bone marrow which results from a greater resorption at the endosteal surface. Under these conditions, the bone cortex becomes thinner. This process, together with increasing porosity of cortical bone and destruction of trabeculae through thinning and perforation, accounts for age-dependent bone loss.

2.3.1 Endocrine factors

Estrogen deficiency

Estrogen is necessary, not only for maximizing peak bone mass in men and women (58–60), but also for maintaining it. It controls bone remodelling in reproductively active women (61, 62) and in ageing men (63, 64). Even a shortening of the luteal phase may be associated with abnormal bone in women (65). Estrogen deficiency and low bone mass also result from conditions such as anorexia nervosa, or exercise-induced amenorrhoea, or from the use of substances that inhibit gonadotropin secretion (53, 66, 67). Estrogen deficiency accelerates

the rate of bone turnover, thereby altering the balance between bone formation and bone resorption, and appears to be the main cause of osteoporosis in women after the fifth decade, and possibly in men. It is thus directly implicated in the age-related increase in the incidence of fragility fractures (62). It is now clearly established that the rate of bone loss does not decrease with age, but continues throughout the whole of life, at least at peripheral skeletal sites (68).

Several cytokines released in the bone marrow increase the rate of bone turnover (20, 21). TNF- α , interleukin-1 and interleukin-6, all stimulate bone resorption in vitro and in vivo, and may initiate the bone loss induced by estrogen deficiency.

In a study using the transgenic mouse model in which the activity of TNF- α was permanently prevented by the presence of high levels of circulating soluble TNF- α receptor 1 (24), no decrease in bone mass or increase in bone turnover was observed after oophorectomy in transgenic mice when compared with control mice, suggesting a key role for TNF- α . While there is evidence that TNF- α , interleukin-1 and interleukin-6 are all involved in bone remodelling and show a considerable degree of interplay (21), only TNF- α appears to be required for the enhanced bone remodelling that occurs after estrogen depletion. This evidence is also consistent with the role of osteoprotegerin, an inhibitor of osteoclast formation. As osteoprotegerin is a soluble member of the TNF receptor superfamily (22), it has the capacity to neutralize the activity of TNF on osteoclastogenesis.

Other endocrine causes of bone loss

In addition to gonadal deficiency, which is an important cause of osteoporosis in men, other endocrine diseases can also cause bone loss by affecting the remodelling of bone (see section 3, Table 5).

Primary hyperparathyroidism and hyperthyroidism increase the rate of bone turnover, thereby inducing bone loss (69, 70). In contrast, excess glucocorticoids reduce bone formation. In addition, administration of glucocorticoids in pharmacological excess may decrease the intestinal absorption of calcium and possibly also its reabsorption by the renal tubules. These latter two effects would lead to a negative calcium balance and result in increased bone resorption through a mechanism which may include secondary hyperparathyroidism (71). Daily doses of 7.5 mg of prednisolone are sufficient to induce skeletal losses (72).

2.3.2 Nutritional factors

Among nutritional factors that cause bone loss, deficiencies in calcium, vitamin D (73–75), and more recently, protein (76) have been

shown to be associated with deficient skeletal growth or accelerated bone loss. Vitamin K deficiency may also be associated with risk of hip fracture (75) (see section 3.5.5).

Dietary intake of phosphates may be increasing in some populations as a result of their use as food additives and the increase in intake of carbonated drinks. These drinks may have a deleterious effect on bone, because they have replaced milk in the diet of some young people, and because high intakes of phosphates stimulate the secretion of PTH, but there is no evidence so far that high phosphate intakes accelerate bone loss in humans.

Calcium intake, vitamin D and osteoporosis

In the elderly, several factors contribute to negative calcium balance. With ageing, calcium intake decreases because of reduced consumption of dairy products, and the absorptive capacity of the intestinal epithelium to adapt to low calcium intake is impaired. Exposure to sunlight and the capacity of the skin to produce vitamin D are also reduced. The capacity of the renal tubule to reabsorb calcium, and its responsiveness to PTH are impaired. Finally, the decrease in glomerular filtration rate observed in the elderly may contribute to chronic hyperparathyroidism, favouring a negative bone mineral balance and thus osteoporosis. Increasing calcium intake is certainly an important strategy which is relatively easier to implement than other possible preventive measures (see section 5.2.1).

Protein intake and osteoporosis

The mechanism whereby a low protein intake has adverse effects on bone (see section 3.5.5) may be due to inadequate production of IGF-1, which exerts anabolic effects on bone mass, not only during growth, but also during adulthood (76). Protein replenishment in patients with hip fracture can improve not only BMD, but also muscle mass and strength. These two variables are important determinants of the likelihood and consequences of falling and thus incidence of osteoporotic fractures.

This observation underlines the importance of weight-bearing in the maintenance of bone mass (77). At the tissue level, immobilization results in bone resorption being greater than bone formation. At the cellular level, immobilization increases bone reabsorption by osteoclasts associated with a decrease in osteoblastic formation (17). The molecular signal(s) perceiving the reduction in mechanical strain associated with immobility has not been identified.

2.4 Determinants of osteoporotic fractures

2.4.1 *Skeletal*

Bone mineral mass

Numerous studies have shown an inverse relationship between BMD and the incidence of osteoporotic fractures. However, other skeletal components also influence bone strength, including both the macro- and microarchitecture of bone.

The bending strength of bones is influenced not only by the amount of bone, but also by its geometrical distribution. In some (but not all) studies, the hip axis length of the femur has been shown to be a predictor of fracture risk independent of BMD.

Other important determinants of bone strength for both cortical and cancellous bone include the degree of mineralization of the matrix as well as the crystal characteristics (78). In cortical bone, mechanical strength is affected by the histological structure, including the presence of primary versus osteonal bone, the orientation of the collagen fibres, the number and orientation of the cement lines, and the presence of microdamage (78). In cancellous bone, mechanical strength is affected by the microstructural arrangement of the trabeculae, including their orientation, connectivity, thickness, and numbers.

The macro- and microarchitectural components of bone strength could explain, at least in part, clinical observations that variations in bone mineral mass are not closely correlated with changes in fracture rate. The risk of fragility fractures also depends on several extraskeletal factors (see section 2.4.2).

Effect of bone remodelling on bone fragility

The degree of bone remodelling, as assessed by the measurement of biochemical indices of bone resorption, has been shown to be a predictor of osteoporotic hip fractures that is independent of BMD (79). This observation suggests that increased bone resorption may increase skeletal fragility because of net bone loss, a deterioration of the bone microarchitecture due to an increase in trabecular plate perforation, or both.

2.4.2 *Extraskeletal*

A fracture is a structural failure of the bone that occurs when the forces applied to it exceed its load-bearing capacity (78). Thus, independently of the size, geometry and physical properties of the bone, the direction and magnitude of the applied load will determine whether a bone will fracture in a given situation (78). Almost all fractures, even those designated as “low trauma” fractures, occur as

the result of some injury. Usually, this is the result of a fall (see section 3.5), or of a specific loading event in some vertebral fractures, such as bending forward to lift a heavy object with arms extended.

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3. Epidemiology and risk factors

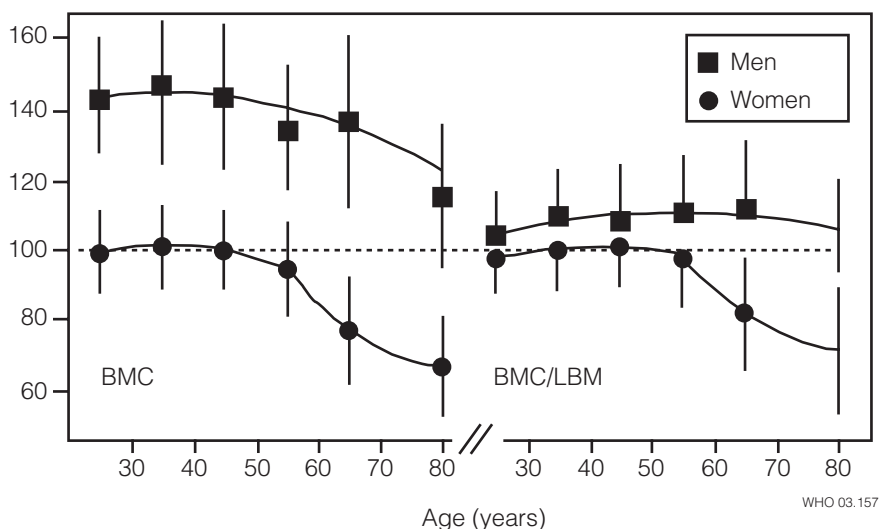
Osteoporosis is characterized by low bone mass (1) which may be the consequence of development of the skeleton during adolescence (low “peak” bone mass) and/or excessive bone loss thereafter. Its clinical and social consequences, however, are the result mainly of the associated fractures. Fractures of the proximal femur (hip), vertebrae (spine) and distal forearm (wrist) are those most commonly associated with osteoporosis, but most fractures in the elderly are related, at least in part, to skeletal fragility (2), and are usually the result of a fall, particularly a sideways fall onto the hip. About one-third of the elderly fall annually; of these, 5% will experience some type of fracture and 1% will suffer a hip fracture (3). In the following sections, the incidence and prevalence of osteoporosis and fractures, and the risk factors for low bone mass and trauma will be reviewed.

3.1 The burden of osteoporosis

The prevalence of low bone density in the general population can be assessed by means of the WHO diagnostic criteria. According to these criteria, women with bone density levels more than 2.5 standard deviations below the young adult reference mean are considered to have osteoporosis (4). Persons with bone density below this threshold who also sustain a fracture meet the definition of “established or severe osteoporosis”. In a large probability sample in the USA, 17% of postmenopausal Caucasian women had osteoporosis of the hip compared to 12% of Hispanic-American women and only 8% of African-American women (5). Assessing additional skeletal sites increases the prevalence of osteoporosis. Thus, about one-third of postmenopausal Caucasian women in the USA have osteoporosis of the hip, spine or forearm (6). Prevalence also increases dramatically with age. Among British women aged 50–59 years, for example, the prevalence of osteoporosis (as defined by a WHO Study Group) at the femoral neck of the hip is 4% and at any site is 15%. These figures rise to 48% and 70%, respectively, in women aged 80 years and over. Less is known about the prevalence of osteoporosis in men, but in the USA 7% of Caucasian, 5% of African-American and 3% of Hispanic-American men have bone density of the hip more than 2.5 standard deviations below the mean for normal young men (5).

The social burden of osteoporosis varies with the incidence of fractures. Fracture rates vary markedly in different countries, being highest in North America and Europe, particularly in Scandinavia (7–9). The risk of osteoporotic fractures is lower in Africa and Asia, but worldwide projections show that it will probably increase

Figure 3
Forearm bone mineral content (percentage of average values for premenopausal women $\pm$ SD) as a function of age in men and women^a



Note: Before the age of 50 years, the differences between the sexes narrow when BMC is adjusted for lean body mass (LBM).

^a Based on data from reference 12.

markedly in the future (10, 11). Osteoporotic fractures are much less common among men than in women because of their peak bone mass at skeletal maturity (12), and their slower rate of bone loss (Figure 3). In addition, the shorter male life expectancy means that they are exposed to the effects of lower BMD for a shorter period. Men lose 15–45% of cancellous bone and 5–15% of cortical bone with advancing age, whereas women lose 35–50% of cancellous bone and 25–30% of cortical bone (13).

Lifetime fracture risk depends both on fracture incidence and life expectancy. At age 50 years the lifetime risk of hip fracture in Scandinavian women exceeds 20%, and is nearly as high in North America. In the USA, the lifetime risk of hip, spine or forearm fracture has been estimated at 40% in Caucasian women from age 50 years onwards and 13% in Caucasian men (2) (Table 2). In the United Kingdom, the lifetime risk of hip fractures among women at age 50 years is 14% while the corresponding figure for men of the same age is 3%. This may be compared with lifetime risks of 11% and 2% for clinically diagnosed vertebral fractures and 13% and 2% for forearm fractures in Caucasian women and men, respectively. These figures

Table 2
Estimated lifetime risk of fracture in Caucasian men and women at age 50 years in Rochester, MN, USA

Fracture site	Lifetime risk of fracture (%) (95% CI)	
	Women	Men
Proximal femur	17.5 (16.8–18.2)	6.0 (5.6–6.5)
Vertebra ^a	15.6 (14.8–16.3)	5.0 (4.6–5.4)
Distal forearm	16.0 (15.7–16.7)	2.5 (2.2–3.1)
Any of the above	39.7 (38.7–40.6)	13.1 (12.4–13.7)

CI, confidence interval.
^a Clinically diagnosed fractures.
 Reproduced from reference 13 with the permission of the publisher.

are conservative since they take account only of vertebral fractures that have come to clinical attention and do not include osteoporotic fractures at other sites (14).

In addition, it has been assumed, in calculations of lifetime risk, that life expectancy will no longer continue to improve; in view of past trends, this is an unreasonable assumption, and any such improvements in life expectancy will increase lifetime fracture risks. Based on current mortality in Swedish men and women, the lifetime risks of hip fracture are 8.1% and 19.5%, respectively, but rise to 11.1% and 22.7%, respectively, if life expectancy does increase as expected (15).

Estimates of the cost of osteoporotic fractures are given in section 6.3.1.

3.2 Common osteoporotic fractures

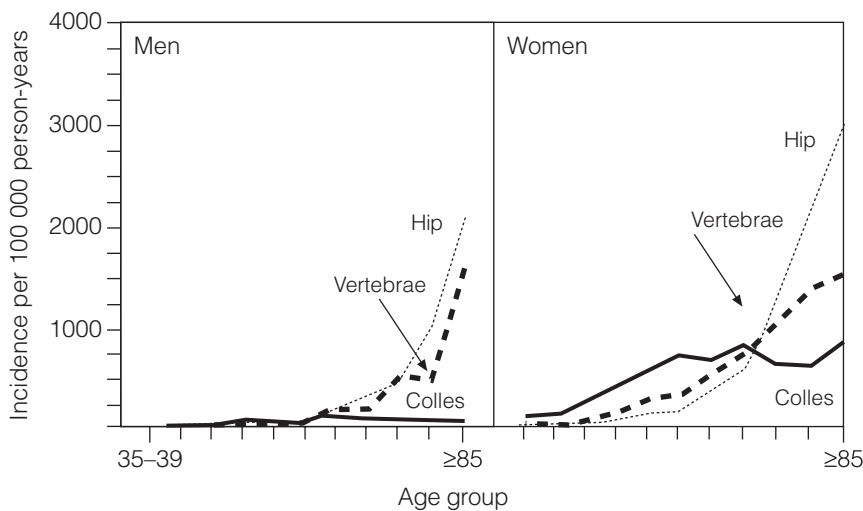
The definition of an osteoporotic fracture is not straightforward. An approach adopted widely is to consider low-energy fractures as being osteoporotic, which has the advantage of recognizing the multifactorial causation of fracture. However, osteoporotic individuals are also more likely to fracture than their normal counterparts following high-energy impact (16). In addition, low-energy fractures differ from those associated with reductions in BMD (17). An alternative approach is to characterize fractures as osteoporotic where they are associated with low bone mass and rising incidence after age 50 years. The most common fractures associated with these conditions are those of the hip, spine and wrist. Fractures of the humerus, ribs, tibia (in women), pelvis and other femoral fractures would be included. Their neglect underestimates the burden of osteoporosis, particularly in younger individuals.

3.2.1 Hip fractures

Hip fractures are the most serious osteoporotic fractures and most of them follow a fall from the standing position, although they may also occur spontaneously (2). They are painful and nearly always necessitate hospitalization. There are, broadly speaking, two types of hip fracture, intracapsular (cervical or femoral neck fractures) and extra-capsular (lateral or trochanteric) fractures, which differ somewhat in both natural history and treatment. Trochanteric fractures are more characteristically osteoporotic, and the increase in age- and sex-specific risk of hip fracture is greater for trochanteric than for cervical fractures, and is more commonly associated with prior fragility fractures. In many countries they occur with equal frequency, though the average age of patients with trochanteric fractures is approximately 5 years older than that for patients with cervical fractures.

As shown in Figure 4, incidence rates for hip fractures increase exponentially with age in both sexes, reaching about 3% annually among Caucasian women aged 85 years and over; rates for Caucasian men of all ages are about half as much (2). Overall, 90% of hip fractures occur among people aged 50 years and over, and 80% occur in women. The average age at which osteoporotic hip fractures occur is about 80 years in developed countries but is less in countries with lower life expectancies. Age-adjusted and sex-adjusted hip fracture

Figure 4
Age-specific incidence rates of hip, vertebral and Colles (forearm) fracture in Rochester, MN, USA^a



WHO 03.158

^a Reproduced from reference 20 with permission from Elsevier.

rates are generally higher in Caucasian than in black or Asian populations (18), although urbanization has led to higher hip fracture rates in Asia and certain parts of Africa. Furthermore, the pronounced female preponderance observed in white populations is not seen among blacks or Asians, in whom male and female rates are similar (19).

3.2.2 **Vertebral fractures**

Epidemiological information on vertebral fractures is limited by the lack of a universally accepted definition of what constitutes a vertebral deformity and because a substantial proportion of such deformities are clinically silent or not due to osteoporosis. Scheuermann disease and vertebral osteoarthritis are common examples of conditions other than osteoporosis that cause vertebral deformities.

Radiographic surveys indicate that 19–26% of postmenopausal Caucasian women have vertebral deformities (21–24), most of which involve the mid-thoracic vertebrae or the thoracolumbar junction, the weakest regions of the spine. Vertebral deformities are as frequent in Asian as Caucasian women (25, 26), but are less common in African-American (27) and Hispanic (28) populations (28). The overall incidence of new vertebral deformities among postmenopausal Caucasian women has been estimated to be approximately three times that of hip fracture, but the incidence of clinically diagnosed vertebral fractures is only about 30% of this figure. The age-adjusted female-to-male incidence ratio for these fractures is about 2:1 (29). However, the prevalence of vertebral deformities in men is as great as it is in women up to age 60 years (24), possibly because some deformities in men are the consequence of occupational stresses rather than fractures. In addition, severe trauma (e.g. motor vehicle accidents), which occur more often in the course of daily activities, may account for over one-third of clinically detected vertebral fractures in men but only about 10% of those in women (24).

3.2.3 **Forearm fractures**

The pattern of occurrence of forearm fractures differs from that of hip or vertebral fractures. The rates reported in many studies increase linearly in white women between the ages of 40 and 65 years and then stabilize (see Figure 4). In some countries, e.g. Sweden, incidence rises progressively with age. In men, the incidence remains constant between the ages of 20 and 80 years and at a much lower rate than in women (2). The reason for the plateau in female incidence in some countries remains obscure, but may relate to a change in the pattern of falling with advancing age (30). As in the case of hip

fracture, the majority of forearm fractures occur in women and around half occur among women aged 65 years and over. Forearm fractures are less frequent in African-American (31, 32), and Japanese populations (33), but there is still a substantial female excess. In Africa and south-east Asia, however, distal forearm fractures are less common and rates for women are little higher than those for men (19, 34).

3.3 Geographical variation

The absolute risk of fractures due to osteoporosis varies markedly from country to country (2, 7–9, 18). The most reliable data available are those for hip fracture, which show that incidence rates vary substantially from one population to another (9, 18). Thus, age-adjusted hip fracture incidence rates are higher among Caucasian residents of Scandinavia than comparable people in North America or Oceania. Even within Europe, hip fracture rates vary more than 7-fold from one country to another (8, 9), and a somewhat less marked variation has also been reported for vertebral fractures (24). The marked variation in fracture incidence within specific countries suggests that environmental factors are important. The higher incidence of hip fractures in urban as opposed to rural districts has been explained on the basis of the lower bone mass of urban residents (35). However, regional differences in the USA do not seem to be accounted for by differences in the levels of physical activity, obesity, cigarette smoking or alcohol consumption or by Scandinavian descent (36). Other factors that may contribute to regional differences include water hardness, sunlight exposure, poverty levels, and the proportion of agricultural land. Further studies are needed to identify the environmental factors responsible for such marked regional differences.

Fracture rates at different skeletal sites tend to be correlated within a given population (Table 3) (2). For example, both forearm and hip fracture rates in the United Kingdom are about 30% lower than those in the USA.

3.4 Secular trends

The financial and health-related costs of osteoporosis will inevitably increase in the future (37), since life expectancy is increasing everywhere with a consequent increase in the number of elderly individuals. The number of individuals aged 65 years or over, currently estimated at 323 million, is expected to reach 1555 million by the year 2050. These demographic changes alone can be expected to cause an increase in the number of hip fractures occurring among people aged

Table 3

Age-adjusted incidence^a (per 100 000 person-years) of distal forearm fractures compared to hip fractures in different populations of persons at age 35 years or over

Geographical locality	Distal forearm		Proximal femur	
	Women	Men	Women	Men
Oslo, Norway	767	202	421	230
Malmö, Sweden	732	178	378	241
Stockholm, Sweden	637	145	340	214
Rochester, Minnesota, USA	410	85	320	177
Trent Region, England	405	97	294	169
Oxford–Dundee, UK	309	73	142	69
Yugoslavia:				
High-calcium area	228	95	44	44
Low-calcium area	196	110	105	94
Tottori, Japan	149	59	108	54
Singapore	59	63	42	73
Nigeria	3	4	1	3

^a Age-adjusted to the population structure of Caucasians 35 years and older in the USA in 1985. Reproduced from reference 2 with the permission of the publisher.

35 years and over throughout the world from about 1.5 million in 1990 to 4.5–6.3 million in 2050 (10, 11). Based on current hip fracture incidence rates in various parts of the world, approximately half of all hip fractures among elderly people in 1990 are believed to have occurred in Europe and North America. By 2050, thanks to rapid ageing of the Asian and Latin American populations, the European and North American contribution will fall to only 25%, and over half of all hip fractures will occur in Asia. It is clear, therefore, that osteoporosis will become a global problem over the next half century and that measures are urgently required to avert this.

These projections may be underestimates because fracture incidence rates in some countries are increasing (38). Although age-adjusted hip fracture rates appear to have levelled off in the northern region of the USA, parts of Sweden and the United Kingdom (39–42), rates in the Hong Kong Special Administrative Region of China rose substantially between 1966 and 1985 (43). Increases in regions other than Europe and North America might cause fracture rates to double to over 8 million by 2050 (11).

There are three possible explanations for these secular trends. First, they may reflect the influence of some increasingly prevalent risk factor for bone density loss or falling, but time trends for a number of possible risk factors, including oophorectomy, hormone replacement

therapy (HRT), cigarette smoking, alcohol consumption and dietary calcium intake, do not match those observed for hip fractures. Physical activity, however, appears to be a likely candidate, since there is ample epidemiological evidence linking inactivity to an increased risk of hip fracture (44, 45), an effect that may be mediated through a decrease in bone density, an increased risk of falls, or both. There may also be important secular trends in environmental factors and the surfaces on to which individuals fall, since urbanization has resulted in a progressive increase in harder surfaces. The second possible explanation for these secular trends is that the elderly population is becoming increasingly frail. The prevalence of disability is known to increase with age, and to be greater among women than men at any age. Since many of the disorders contributing to frailty are independently associated with osteoporosis and the likelihood of falling, this tendency may have contributed to the secular increases in fracture risk in the developed countries during the twentieth century. Finally, the trends may be the consequence of cohort phenomenon, i.e. an adverse influence on bone mass or risk of falling which acted at an earlier time is now being manifested as an increase in the incidence of fractures in successive generations of the elderly (46). Such generational effects explain some of the secular trends in adult height during the twentieth century, and similar effects on the skeleton are likely, and may be mediated through intrauterine or early postnatal programming, as well as childhood nutrition and physical activity.

3.5 Risk factors for osteoporotic fracture

Although many risk factors for osteoporotic fracture have been identified, risk factors for different fractures may differ. For example, an early menopause is a strong risk factor for vertebral fractures, but not for hip fracture in later life. Risk factors may be causally related or indirect. While the former are amenable to personal modification, environmental or therapeutic manipulation, even indirect factors may be useful in identifying individuals at high risk. The mechanisms whereby these risk factors give rise to increased fragility are reviewed in section 2.

3.5.1 *Trauma*

Fractures occur when skeletal loads, whether from trauma or the activities of daily living in the case of some spine fractures, exceed the breaking strength of bone. Falls are the most common cause of traumatic osteoporotic fractures. The annual risk of falling increases from about 20% in women aged 35–49 years to nearly 50% in women aged 85 years and over, and is 33% in elderly men (47). Although

environmental hazards play a role in many falls, up to half the falls among the elderly are associated with organic dysfunction, including diminished perceptions of the lower extremities and postural control, gait abnormalities, muscular weakness, decreased reflexes or poor vision. In addition, chronic illnesses such as neurological disorders, heart disease, stroke, urinary incontinence, depression and impaired cognitive function increase the risk of falling. The proportion of falls associated with these problems increases with age (48), and the risk of falling is correlated with the number of comorbid conditions present. Medications such as hypnotics, antidepressants or sedatives are also associated with falls (49). Potential hazards in the home include slippery floors, unstable furniture and poor lighting (49).

The mechanics of falling are such that only about 5% of falls lead to a fracture. The likelihood of a hip fracture depends on the orientation of the fall (backwards or to the side), and is greater the higher the potential energy of the faller, the lesser the amount of soft tissue padding over the hip and the lower the bone density of the proximal femur (49, 50).

3.5.2 **Low bone density**

Risk factors for low bone density include inadequate peak bone mass and excessive bone loss (51). In addition to the accelerated bone loss seen at the menopause, bone loss may also result from age-related conditions such as reduced calcium absorption from the gut and secondary hyperparathyroidism (see section 2.3.2). In addition, certain medical and surgical conditions can produce so-called “secondary” osteoporosis. In the most comprehensive study to date, the Study of Osteoporotic Fractures (52) (Table 4), the determinants of BMD at various skeletal sites were assessed in a large number of Caucasian or Asian-American women aged 65 years or over, and included greater age at menopause, estrogen or thiazide use, non-insulin-dependent diabetes (NIDDM), and greater height, weight, strength and dietary calcium intake, all of which were positively associated with greater BMD at the distal radius. In contrast, older age, cigarette smoking, caffeine intake, prior gastric surgery and maternal history of fracture were negatively associated with BMD at that site (53). For the spine, greater weight, older age at menopause, a history of osteoarthritis, greater physical activity, moderate consumption of alcoholic beverages, treatment with diuretics and current HRT were associated with greater BMD, while later age at menarche and a maternal history of fracture were associated with lower BMD (52). Increasing age positively correlated with spinal BMD in these elderly women, probably because of hypertrophic changes in the spine. Greater BMD of the

Table 4
Risk factors (–) and protective factors (+) for axial and appendicular bone mineral density in women at age 65 years and over^a

Variable	Skeletal site		
	Lumbar spine (DXA)	Femoral neck (DXA)	Distal radius (SPA)
Age		--	--
Weight	+++	+++	+++
Fracture in mother	--	--	--
Age at menopause	+	+	++
Estrogen use	+++	+++	+++
Quadriceps strength		++	
Grip strength			+++
Thiazide use	+++	++	+++
Non-thiazide diuretic use	++		
Current smoker			--
Number of alcoholic drinks in lifetime	+		
Dietary calcium intake		++	+
Lifetime caffeine intake			–
Non-insulin-dependent diabetes mellitus		+++	+++
Gastric surgery			--
Recent or past physical activity	+	+	

DXA, dual-energy X-ray absorptiometry; SPA, single-energy photon absorptiometry.
^a The strength of the correlations from multivariate analyses is indicated by the number of symbols: three symbols indicate 3% or greater change in bone mineral density per unit change in the variable; two symbols, a 1–3% change; and one symbol, a change of less than 1%.
 Based on data from reference 52.

femoral neck was positively associated with most of the same factors as those listed for the spine, together with quadriceps strength, calcium intake, and a history of NIDDM (52). A history of maternal fracture and of prior wrist fracture was associated with low femoral neck BMD. Greater age was a risk factor for low BMD of the femoral neck, as it was for low BMD of the radius. Risk factors are reviewed in greater detail below.

3.5.3 Previous fracture

The occurrence of one osteoporotic fracture may increase the risk of future fractures. Thus in both men and women who have suffered a distal fracture of the forearm, the risk of subsequent fractures of the proximal femur and other skeletal sites is approximately doubled (54–57). In recent cohort studies, a 1.8–3.8-fold excess of subsequent hip fractures has been reported among women with a prevalent vertebral

fracture at cohort inception (58, 59), accompanied by even greater increases in the risk of additional vertebral fractures (60). In a comprehensive analysis (61), incident clinically diagnosed vertebral fractures significantly increased the risk of any future fracture (relative risk (RR) = 2.8; 95% CI 2.5–3.1). The greatest increase was observed for additional vertebral fracture (RR = 12.6; 95% CI 11–14), while lesser increases were also observed for hip (RR = 2.3; 95% CI 1.8–2.9) and forearm fractures (RR = 1.6; 95% CI 1.0–2.4).

3.5.4 **Genetics**

Up to 50% of the variance in peak bone mass and some aspects of bone architecture and geometry relevant to bone strength may be determined genetically (62, 63) (see section 2.2.6). A family history of fragility fracture, and particularly of hip fracture, can be used in the risk assessment of patients (see section 4.4.4).

3.5.5 **Nutrition**

Dietary factors influence peak bone mass, age-related bone loss and fracture risk. Calcium and vitamin D are particularly important since deficiencies are potentially correctable (61).

Calcium

Intervention and cross-sectional studies have reported a positive effect of a higher intake of calcium on bone mass in children and adolescents. In a prospective study, dietary calcium intake in childhood was positively related to BMD in young women (64, 65). In a meta-analysis of 33 studies, an association between higher calcium intake and higher bone mass was found in premenopausal women; however, no conclusions could be drawn about this relationship in men because of insufficient data (66). In general, the most consistent effects of calcium supplementation are observed in the appendicular skeleton, while effects on spinal bone appear to be transient. Older women seem to be more responsive to such supplementation than younger postmenopausal women (see section 5.2.1).

The relationship between calcium intake and fracture rate is less clear. While inverse correlations between dietary calcium intake and fracture (mainly of the hip) have been found in some studies, no significant correlation has been found in others and some have even shown a positive correlation between calcium intake and hip fracture. However, in a recent meta-analysis, it was reported that each additional gram of calcium in the diet was associated with a 25% reduction in hip fracture risk (67).

Vitamin D

Severe and prolonged deficiency of vitamin D results in rickets in children and osteomalacia in adults, conditions characterized by defective mineralization of bone. Osteomalacia will aggravate osteoporosis, since both increase the risk of fracture. Vitamin D deficiency is rare in Europe and the USA, but is still common in the Middle East and the Asian subcontinent.

Lesser degrees of vitamin D deficiency (vitamin D insufficiency) are associated with an increase in PTH production, resulting in increased bone turnover and bone loss in the absence of any significant mineralization defect (68). Low levels of circulating vitamin D are common in elderly populations in many regions of the world and may contribute to fractures, particularly at the hip (see also section 2.3.2). A positive association between serum $1\alpha,25$ -dihydroxycholecalciferol concentration and BMD was found in middle-aged and elderly women, whereas an inverse relationship between serum PTH levels and BMD has been reported. Vitamin D supplementation prevents the reduction in BMD that occurs during the winter months in normal subjects. Trials of the administration of calcium and vitamin D to institutionalized elderly people have shown that relatively small amounts of vitamin D reduce non-vertebral fracture rates (see section 5.2.2) (69). Maintaining an adequate vitamin D status in the elderly may also improve muscle strength and reduce both the risk and consequences of falling (70).

Protein

Malnutrition continues to be common, particularly in parts of Africa and Asia. Low protein intake is an important determinant of peak bone mass and therefore of the risk of osteoporosis in later life (71). Elsewhere, the prevalence of malnutrition and undernutrition increase with advancing age and in patients with hip fracture. In the elderly, an association between low protein intake, low BMD and reduced mobility has been reported (72). This does not seem to be due to ageing itself, since healthy active elderly people and young adults are nutritionally not very different, in contrast to the acutely and chronically ill elderly population in whom signs of malnutrition are common (73, 74). Undernutrition may increase the propensity to falls both by impairing coordination and reducing muscle strength. It is also an important determinant of the consequences of falling, since a reduction in the protective layer of soft tissue padding decreases the force required to fracture an osteoporotic hip (73–76).

Phosphate

A high dietary intake of phosphate in combination with a low intake of calcium increases serum PTH concentrations and may reduce BMD.

Vitamin K

Low plasma levels of vitamin K₁ and K₂ have been reported in patients with hip fracture. Vitamin K is essential for the production of gamma-carboxylated glutamyl residues present in several coagulation factors and bone proteins, particularly osteocalcin (65, 77, 78). Vitamin K deficiency can be assessed by measuring the undercarboxylated fraction of osteocalcin. This fraction increases with age and is therefore negatively related to BMD in elderly women. Undercarboxylated osteocalcin has been reported to be a predictor of hip fracture. However, protein–energy malnutrition is usually associated with multiple deficiencies so that the particular contribution of vitamin K deficiency to bone loss in undernourished patients sustaining hip fracture is unknown.

Magnesium and other trace elements and vitamins

Magnesium interferes with both the production and action of PTH, and thus indirectly affects bone metabolism. However, a specific role of magnesium in the maintenance of bone mass during adulthood has not yet been identified. Several trace elements are required for normal bone metabolism. Various animal and/or ecological studies in humans suggest that aluminum, boron, copper, fluoride (at doses lower than those used in the treatment of osteoporosis), manganese, silicon, and zinc, as well as vitamins B₆, B₁₂ and C, may all play a protective role in the normal metabolism of bone tissue (79). Selective intervention studies are still required to identify their respective roles in the maintenance of bone mass, particularly in the elderly.

3.5.6 Physical inactivity

Immobility is an important cause of bone loss, and its detrimental effect on bone mass is far greater than the beneficial effect of additional exercise in an already ambulatory subject (80). Enforced immobility in healthy volunteers decreases bone mineral mass, as do motor deficits due to neurological disorders such as hemiplegia or paraplegia. Bone mineral mass also decreases during space flights despite vigorous physical exercise.

In contrast, bone density increases in response to physical loading and mechanical stress. In many cross-sectional studies, a beneficial effect of weight-bearing exercise on peak bone mass has been reported (81,

82). The observation that retired adult gymnasts have higher BMD than age-matched sedentary controls suggests the benefits of physical activity outlast the termination of such activity (82), and the results of randomized controlled trials suggest that certain forms of exercise may retard bone loss. These studies also show that the skeletal site which is maximally loaded demonstrates the greatest effect.

The type of loading also influences skeletal response. High-impact exercise appears to result in greater increases in bone density than low-impact ones. A recent meta-analysis of 18 studies of postmenopausal women reported a significant protective effect against bone loss at the lumbar spine, but a less clear effect at the femoral neck (45). Other studies, although not randomized, have demonstrated a relationship between customary physical inactivity in the elderly and a lower risk of hip and vertebral fracture. This effect may, in part, be due to the reduced risk of falling, rather than to increased bone strength alone.

3.5.7 *Cigarette smoking*

Cigarette smoking reduces BMD as a result, inter alia, of the consequent earlier menopause, reduced body weight and enhanced metabolic breakdown of exogenous estrogen in women (83). In contrast to the large number of studies documenting the adverse effects of cigarette smoking on peak bone mass, few studies of the relationship between cigarette smoking and bone loss have been carried out. A recent meta-analysis of the results of 48 published studies (84) showed that, although no significant difference in bone density at age 50 years between smokers and non-smokers existed, bone density in women who smoked diminished by about 2% for each 10-year increase in age, with a 6% difference at age 80 years between smokers and non-smokers. These data are borne out by longitudinal observational studies. Epidemiological studies have also shown an independent effect of cigarette smoking on the risk of hip fracture (84).

3.5.8 *Alcohol consumption*

Studies of people dependent on alcohol have suggested that high levels of alcohol consumption may be detrimental to bone, possibly as a result, inter alia, of protein and calcium metabolism, mobility, gonadal function and a direct toxic effect on the osteoblast (see section 2.3.3). However, moderate consumption of alcohol has not consistently been associated with increased risk of fracture or reduced bone density. In postmenopausal women, alcohol consumption appears to reduce both bone loss at the hip and the risk of vertebral fracture (83, 85).

3.5.9 **Body mass index**

Low body mass index (BMI) is associated with lower peak bone mass, and an adverse influence on bone loss (86, 87). This may be the consequence of reduced peripheral estrogen production by adipose tissue among thin women, less mechanical loading of the skeleton, and metabolic influences on body composition. Excessive leanness is also a risk factor for hip and vertebral fracture, and longitudinal epidemiological studies have shown that accelerated weight loss is an important determinant of the risk of hip fracture (88). In Europeans, the risk of hip fracture is increased below a threshold BMI of 19 kg/m^2 (89, 90). It is not known whether this threshold is also applicable to other populations.

3.5.10 **Sex hormone deficiency**

Primary hypogonadism in both sexes is associated with low bone mass, and decline in estrogen production at the menopause is the most important factor contributing to osteoporosis in later life (91, 92). In addition, secondary amenorrhoea, as the result, e.g. of anorexia nervosa, excessive exercise or chronic disease, results in lower peak bone mass and increased risk of osteoporosis. Late menarche may be associated with lower peak bone mass and higher fracture risk (90). Finally, some studies indicate that the use of oral contraceptives may be associated with higher bone mass, although this finding has not been universal. A premature menopause, particularly when surgically induced before age 45 years, is a strong determinant of bone density and increased risk of fracture.

3.5.11 **Other causes of osteoporosis**

An increased risk of osteoporosis is associated with a host of other diseases and disorders (91), including endocrine and metabolic disorders, and malignant disease (Table 5), and with the use of certain drugs (Table 6).

3.6 **Conclusions**

Osteoporosis is a common condition which is clinically important because of its association with fractures. The incidence of osteoporotic fractures depends both on bone strength and propensity to trauma. Bone mass is a key determinant of bone strength, and depends both on peak bone mass at early adulthood and on the subsequent rate of bone loss. Up to 50% of the variation in peak bone mass may be genetically determined, and polymorphisms for several candidate genes are currently being investigated. Sex hormone

Table 5

Diseases and disorders associated with an increased risk of generalized osteoporosis in adults

Endocrine

Thyrotoxicosis
 Hyperparathyroidism
 Cushing syndrome
 Insulin-dependent diabetes mellitus
 Adrenal atrophy and Addison disease
 Ectopic adrenocorticotrophic hormone syndrome
 Sarcoidosis (ectopic calcitriol production)

Gastrointestinal

Severe liver disease — especially primary biliary cirrhosis
 Gastrectomy
 Malabsorption syndromes including coeliac disease

Metabolic and nutritional

Haemophilia
 Hypophosphatasia
 Congenital erythrocytic porphyria
 Chronic renal disease
 Idiopathic hypercalciuria
 Haemochromatosis
 Osteogenesis imperfecta
 Mastocytosis
 Amyloidosis
 Thalassaemia and chronic haemolytic disease
 Parenteral nutrition

Neoplasia

Myelomatosis
 Tumour secretion of parathyroid hormone-related peptide
 Lymphoma and leukaemia

Other

Chronic obstructive pulmonary disease
 Epidermolysis bullosa
 Pregnancy

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deficiency is a key factor in the pathogenesis of osteoporosis in post-menopausal women and may also contribute to bone loss in ageing men (92). The use of glucocorticosteroids is also an important cause of accelerated bone loss and osteoporosis. In addition, nutrition, physical activity, alcohol consumption and cigarette smoking also affect bone mass. Modification of these factors on a population-wide basis could have a significant impact on the incidence of osteoporotic fracture in future generations (see section 6.4).

Table 6

Drugs associated with an increased risk of osteoporosis

Glucocorticosteroids and adrenocorticotrophin
 Thyroxine
 Anticonvulsants
 Depo-provera
 Heparin
 Lithium
 Cytotoxic drugs
 Gonadotrophin-releasing hormone agonists
 Tamoxifen (premenopausal use)
 Aluminium
 Vitamin D toxicity
 Hyperoxia

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4. **Diagnosis and assessment**

4.1 **Introduction**

Increasing awareness of osteoporosis and the development of treatments of proven efficacy is likely to increase the demand for the care of patients with this condition. This in turn will require more facilities for the diagnosis and assessment of osteoporosis, and particularly for the measurement of bone mineral, which is central to the definition of osteoporosis.

The internationally agreed description of osteoporosis is that it is 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 (1, 2). This view of osteoporosis embodies the concept that bone mass is an important factor in the risk of fracture, but that other skeletal abnormalities contribute to skeletal fragility, while some non-skeletal factors also affect fracture risk. The assessment of fracture risk should therefore encompass all these factors. This section summarizes and updates the extent to which this is possible in clinical practice (3).

4.2 **Methods of measuring bone mass or density**

4.2.1 ***Single- and dual-energy X-ray absorptiometry***

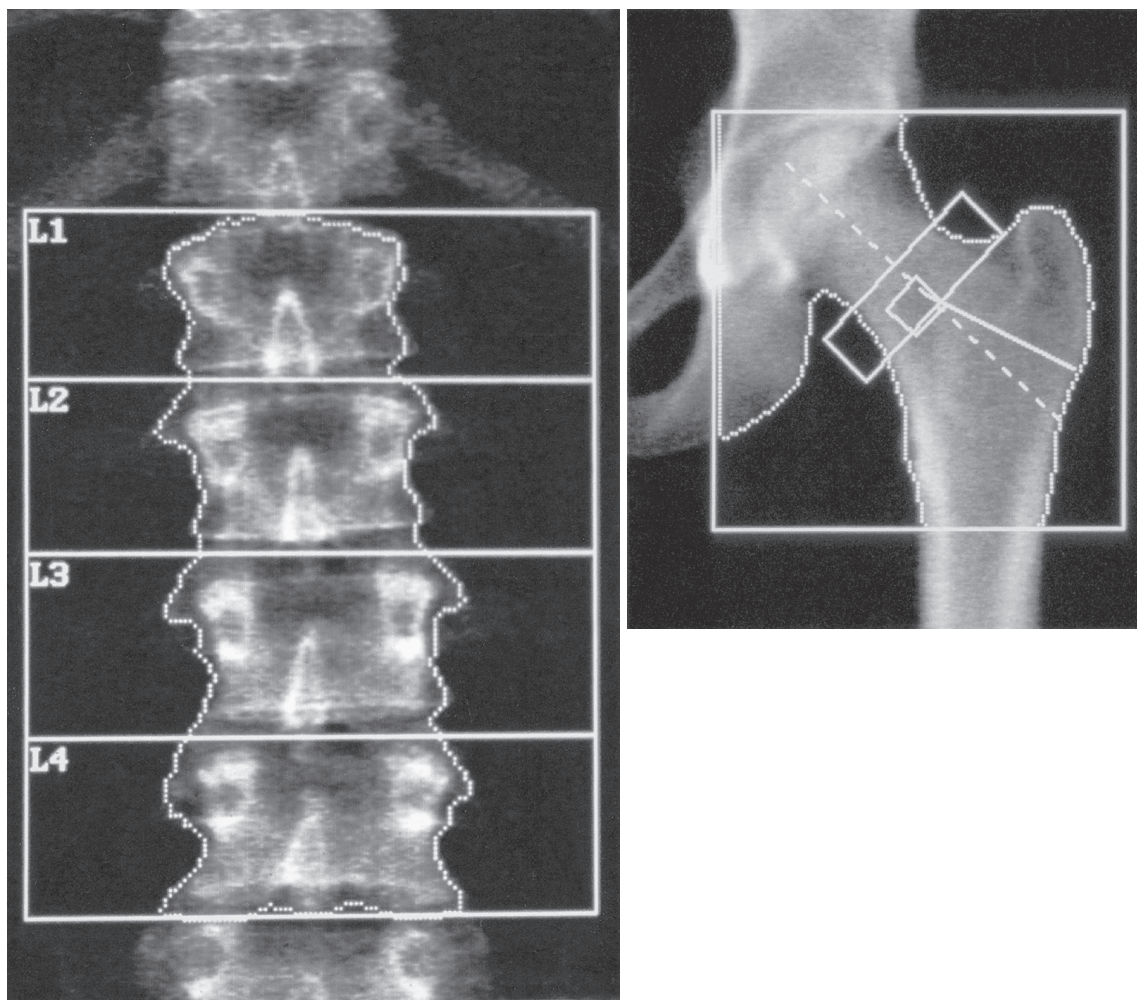
Single and dual X-ray absorptiometry (SXA, DXA) are methods of assessing the mineral content of the whole skeleton, as well as of specific sites, including those most vulnerable to fracture (4). The term “bone mineral content” describes the amount of mineral in the specific bone site scanned, from which a value for BMD can be derived by dividing the bone mineral content by the area or volume measured. With both SXA and DXA this is an areal density rather than a true volumetric density, since the scan is two-dimensional, as illustrated in Figure 5. The results of a typical scan of the lumbar spine in a 53-year-old perimenopausal woman are shown in Table 7.

In single-energy absorptiometry, bone mineral is measured at appendicular sites, such as the heel or wrist. SXA is widely available for forearm mineral measurements, and is more precise than single-photon absorptiometry (SPA), which also has the disadvantage of requiring the use of isotopes such as ¹²⁵I.

Dual-energy absorptiometry (dual-photon absorptiometry (DPA) or DXA) measures bone mineral at sites such as the spine and hip; it can also measure total body bone mineral. SPA and SXA cannot be used for these sites. DXA is also being increasingly used for measurements at appendicular sites.

Figure 5

Two-dimensional DXA scan of the lumbar spine and hip in a young healthy adult



Of the many techniques developed to assess bone mass, bone mineral or other related aspects of skeletal mass or structure, the most highly developed technically and the most thoroughly validated biologically is DXA, which is regarded as the “gold standard”, with which the performance characteristics of less well-established techniques can be compared. All these techniques are used for the diagnosis of osteoporosis, prognosis (fracture prediction), monitoring the natural history of the disorder, and assessing response to treatment.

Table 7
Measurements made from anteroposterior scan using DXA at the lumbar spine in a perimenopausal woman aged 53 years^a

Region	Area (cm ²)	BMC (g)	BMD (g/cm ²)	T-score (SD units)	Z-score (SD units)
L1	12.24	10.29	0.841		
L2	13.03	13.04	1.000		
L3	14.51	15.00	1.034		
L4	15.08	15.81	1.048		
Total	54.86	54.14	0.987	-0.55	+0.41

^a BMD values are expressed in relation to the young adult mean (T-score) or age-matched controls (Z-score).

4.2.2 **Ultrasound**

Quantitative ultrasound (QUS) has recently been used to assess skeletal status in osteoporosis. The methods thoroughly evaluated are broad-band ultrasound attenuation (BUA) and speed of sound (SOS) (or ultrasound velocity) at the heel. These methods have the advantage in that they do not involve ionizing radiation and may provide information on the structural organization of bone in addition to bone mass.

QUS techniques have been evaluated in a large number of studies (5, 6). They cannot at the present time provide diagnostic criteria for osteoporosis, but on current evidence they are suitable for the assessment of fracture risk in elderly women, and their prognostic value for future hip fracture is reportedly as good as that of several other peripheral assessments (7, 8). Performance is less satisfactory in other uses. Their use has been best established for calcaneal systems. Its low cost and portability make QUS more attractive for use in assessing the risk of fractures in larger populations than may be appropriate for bone densitometry by X-ray absorptiometry.

4.2.3 **Computed tomography**

Quantitative computed tomography (QCT) has been applied both to the appendicular skeleton and to the spine (9, 10), but not yet to the proximal femur, although this is likely to change with the increasing use of spiral CT scanners. Cancellous bone in the spine and radius is highly suitable for assessment by QCT. Conventional whole body CT scanners, which typically generate density information in terms of Hounsfield units, need to be transformed to convert their results into units relevant to BMD. For spine QCT, the patient is usually scanned simultaneously with a calibration phantom for automatic

standardization. Dedicated equipment for assessing density at peripheral sites (pQCT) is widely used in Europe (11). The major advantage of QCT in the assessment of cancellous bone density, as compared with DXA, is that it measures true volumetric density, rather than providing an area-adjusted result as does DXA. Cancellous bone is more responsive to many interventions than is cortical bone, so that this technique is also suitable for monitoring treatment (4). It is also unaffected by degenerative disease, which is a particular problem with spinal DXA. Although QCT also provides information on the shape and macroarchitecture of bone, the resolution of cancellous bone structure is less than optimal. Its major disadvantages are high radiation exposure, difficulties with quality control and high cost compared with DXA.

4.2.4 **Radiography**

Osteoporosis can often be diagnosed by visual inspection of plain radiographs, albeit with low sensitivity (see section 4.4.2). In addition, some quantitative techniques may be useful in assessing risk. The most widely used is the estimate of the cortical width of the second, third and fourth metacarpals. Since the size of tubular bones increases with age, thinning of the cortex represents an increase in net endocortical bone resorption. The ratio of the cortical width to the total width or of the cortical area to the total cross-sectional area are therefore commonly used indices (12). Evaluation can be improved by magnification and the use of fine-grain films. Another technique is radiographic absorptiometry using a step-wedge fountain incorporated into the film, thus permitting an estimate of areal density to be made. Common sites of assessment include the metacarpals, the distal phalanges and the distal forearm. Both absorptiometry and morphometry have been used for many years, but their usefulness in assessing fracture risk is only now being validated in prospective studies.

In recent years it has become apparent that vertebral deformity is a very strong risk factor for subsequent fractures, both at new vertebral sites and at other sites susceptible to osteoporosis. There is, therefore, great interest in identifying vertebral deformities due to osteoporosis that may not have otherwise come to clinical attention.

4.2.5 **Magnetic resonance imaging**

Magnetic resonance imaging (MRI) initially appeared unsuitable for assessing bone, which emits a rapidly decaying signal thanks to its solid crystalline structure that prevents protons in the matrix from aligning themselves within the magnetic field. However, interest has

grown with the realization that X-ray CT will never be able to resolve the microstructure of cancellous bone fully because of the unacceptably high radiation dose that would be required. Although MRI provides no direct information on density, with the positive background given by all types of bone marrow, it provides some resolution of the internal structure of cancellous bone (4, 10). At present, MRI investigation of the skeleton remains a research procedure because of its high costs and complexity.

4.3 Diagnosis

The most straightforward approach to the diagnosis of osteoporosis by bone density measurements is to define a threshold, namely a cut-off point for BMD that will encompass most patients with osteoporotic fractures. Bone density measurements are, however, also used to assess future risk of fracture, so that more than one threshold will be needed.

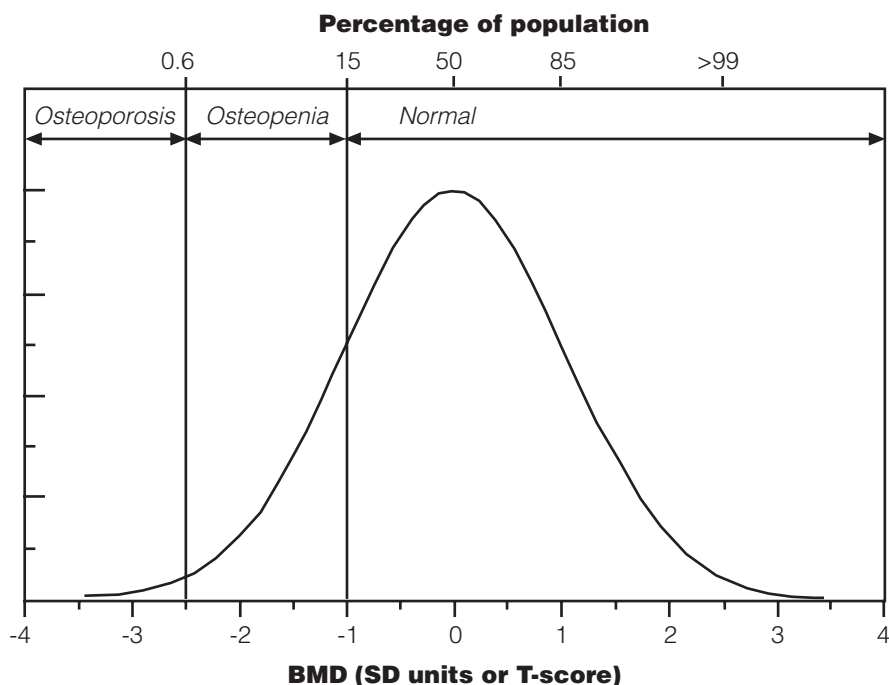
4.3.1 Thresholds

Skeletal mass and density remain relatively constant once growth has ceased, until approximately age 50 years in females and 65 years in males (13). The distribution of bone mineral content or density in young healthy adults (peak bone mass) is approximately normal irrespective of the measurement technique used. With this distribution, individual bone density values are expressed in relation to a reference population in standard deviation units. This reduces the effects of differences in calibration between instruments. Standard deviation units used in relation to the young healthy population are called T-scores.

The following four general diagnostic categories for women have been proposed by a WHO Study Group based on measurements by DXA (14):

- *Normal*. A value of BMD within 1 standard deviation of the young adult reference mean (T-score ≥ -1).
- *Low bone mass (osteopenia)*. A value of BMD more than 1 standard deviation below the young adult mean, but less than 2 standard deviations below this value (T-score < -1 and > -2.5).
- *Osteoporosis*. A value of BMD 2.5 standard deviations or more below the young adult mean (T-score ≤ -2.5).
- *Severe osteoporosis (established osteoporosis)*. A value of BMD 2.5 standard deviations or more below the young adult mean in the presence of one or more fragility fractures.

Figure 6
Distribution of BMD in young healthy women aged 30–40 years^a



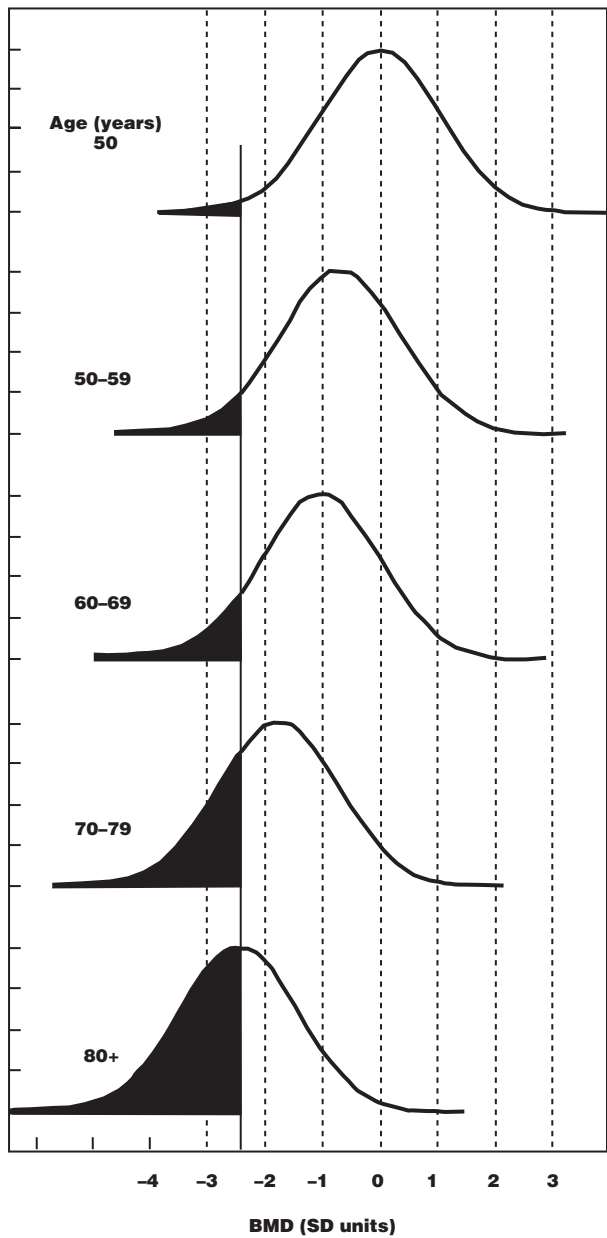
WHO 03.160

Because the distribution of bone density is normal, approximately 15% of the population have a T-score of -1 or lower (low bone mass or osteopenia) and about 0.6% of the population have a T-score below -2.5 (osteoporosis).

In women, bone loss occurs predominantly after the menopause. In the young healthy population, about 15% of women will have T-scores less than -1 and thus meet the criteria for low bone mass or osteopenia (Figure 6). By this definition, approximately 0.6% of the young healthy population have T-scores of -2.5 or less and thus have osteoporosis.

Since the distribution of BMD in the population is normal, the proportion of women affected by osteoporosis at any one site increases markedly with age in much the same way as fracture risk increases with age (15) (Figure 7). Indeed, the increase in prevalence is approximately exponential and is in line with the increasing incidence of many osteoporotic fractures among ageing women. The extent of the problem can be seen from Table 8. For example, the prevalence of osteoporosis of the hip in Caucasian women aged 50 years or over is about 1 in 6, comparable to the lifetime risk of hip fracture. At any of the most vulnerable sites, i.e. spine, wrist and hip, the prevalence is

Figure 7
Distribution of BMD in women at different ages, and the prevalence of osteoporosis^a



WHO 03.161

BMD is normally distributed at all ages, but values decrease progressively with age. The proportion of patients with osteoporosis increases approximately exponentially with age.

^a Reproduced from reference 15 with permission from the American Society for Bone and Mineral Research.

Table 8
Prevalence of osteoporosis in Western women assessed by measurements of BMD at the hip alone, or hip, spine and forearm combined

Age range (years)	Osteoporosis site	
	Any site (%)	Hip alone (%)
30–39	<1	<1
40–49	<1	<1
50–59	14.8	3.9
60–69	21.6	8.0
70–79	38.5	24.5
80+	70.0	47.6
50+	30.3	16.2

Reproduced from reference 14 with the permission of the publisher.

30–40% in postmenopausal women, equivalent to the lifetime risk of any of these fractures (16).

4.3.2 Sites and techniques

With the introduction of a working definition of osteoporosis, several problems have arisen in its application to epidemiology, clinical trials and patient care. The first is the plethora of new measurement techniques applied to many different sites, so that the same T-score derived from different sites and techniques yields different information on fracture risk. These differences arise from differences in the gradient of risk from the various techniques used to predict fracture (17, 18), discrepancies in the population standard deviation at different sites and with different equipment (19, 20), and differences in the apparent rates of bone loss with age (21). A second problem is that intersite correlations, though usually statistically significant, are inadequate for prediction (22–24) because of biological variation and measurement inaccuracy (17).

As a result, T-scores obtained by different techniques and at different sites cannot be used interchangeably. A “gold standard” for diagnosis should therefore be based on a particular site and technology. Measurements of T-scores at the hip are the best predictors of hip fracture, and this has been well established in many prospective studies (25). Moreover, the hip is the site of greatest biological and clinical relevance, since hip fracture is the dominant complication of osteoporosis in terms of morbidity and cost. The T-score measured at the hip with DXA therefore provides the best diagnostic criteria (17). The same holds true in principle for many other multifactorial diseases. For example, in hypertension, measurements made at the leg

may differ substantially from those made at the arm. In this field, it is appropriate to select a standardized site for the purpose of diagnosis, but this does not prevent the use of other techniques for risk assessment.

Similarly, in osteoporosis, these considerations should not be taken to imply that other techniques are not useful where they have been shown to provide information on fracture risk. The selection of a standardized site and technology for diagnosis does not preclude a valuable role for other techniques in the assessment of fracture risk. For other sites and techniques, however, deviations of measurements from normal values should be expressed in units of measurement or units of risk (26).

Problems will arise in some countries, e.g. Brazil and the USA, where diagnosis is linked to reimbursement of costs. To facilitate reimbursement for densitometry, it will be necessary to replace T-scores by measurements that lie in the range of “unacceptable risk of fracture”. This is true for all techniques, including DXA at the hip, since the absolute risk of fracture at a given T-score varies markedly with age. These considerations demand that both clinicians and regulatory agencies should accept the notion that a given risk of osteoporotic fracture provides a diagnostic or intervention threshold.

4.3.3 ***Diagnosis in men***

Diagnostic cut-off values for men are not well established. However, population studies and a prospective study have both suggested that the cut-off value for spine or hip BMD used in women, i.e. 2.5 standard deviations or more below the average, can be used for the diagnosis of osteoporosis in men since the risks of hip and vertebral fractures are similar in men and women for any given BMD (27–30). This threshold value may require adjustment for body size in some populations (31).

4.3.4 ***Accuracy and diagnosis***

The ability of DXA and of other techniques to provide a diagnosis of osteoporosis depends critically on their performance characteristics (Table 9). In the *diagnostic* use of these techniques, accuracy is the degree to which a given test measures BMD correctly and thus the extent to which it correctly stratifies an individual within the normal distribution for BMD. The accuracy of DXA at the hip exceeds 90%. Residual errors arise for a variety of reasons, related to the technique itself and the manner in which the technique is applied.

Table 9
Performance characteristics of various techniques of bone mass measurement at various sites

Technique	Site	Cancellous bone (%)	Precision error in vivo (%)	Accuracy error in vivo (%)	Effective dose equivalent (μSv)
SXA	Forearm — distal	5	1–2	2–5	<1
	Forearm ultradistal	40	1–2	2–5	<1
	Heel	95	1–2	2–5	<1
DXA	Lumbar — AP	50	1–1.5	5–8	1
	Lumbar — lateral	90	2–3	5–10	3
	Proximal — femur	40	1.5–3	5–8	1
	Forearm	5	1	5	<1
	Total body	20	1	3	3
QCT	Spine — trabecular	100	2–4	5–15	50
	Spine — integral	75	2–4	4–8	50
pQCT	Radius — trabecular	100	1–2	?	1
	Radius — total	40	1–2	2–8	1
QUS: SOS	Calcaneus/tibia	95/0	0.3–1.2	?	0
QUS: BUA	Calcaneus	95	1.3–3.8	?	0

BUA, broad-band ultrasound attenuation; DXA, dual x-ray absorptiometry; QCT, quantitative computed tomography; SOS, speed of sound; SXA, single x-ray absorptiometry. Based on data from references 4 and 14.

Standard DXA techniques use a two-dimensional projection and do not, therefore, measure BMD (g/cm^3), but rather areal density (g/cm^2). Thus, the size of the bone affects the apparent density since the relationship between area and volume is non-linear. Paradoxically, this error may improve the value of BMD for fracture prediction, since bone size is also a determinant of skeletal strength. Systematic inaccuracies with DXA occur particularly at the spine since the vertebrae are irregular in shape and apparent density, and mineral content will depend, in part, on the algorithm used for edge detection. This systematic error in measured BMD when different machines are used can be partially avoided by using T-scores.

Non-systematic errors of accuracy also occur which mean that ash weight will be predicted less confidently from BMD. The largest source of error arises because of variable soft tissue density (17).

The sources of error in the diagnosis of osteoporosis by means of DXA are listed in Table 10 (32). Thus osteomalacia, a complication of poor nutrition in the elderly, causes bone mass to be underestimated. Osteoarthritis at the spine or the hip is common in the elderly, and contributes to the density measurement but not necessarily to skeletal strength. Heterogeneity of density due to osteoarthritis or previous fracture can often be detected on the scan and sometimes excluded from the analysis. In the case of the hip, other regions of

Table 10

Sources of error in the diagnosis of osteoporosis by DXA

Osteomalacia
Osteoarthritis (spine but also the hip)
Soft tissue calcification (especially the spine)
Overlying metal objects
Contrast media
Previous fracture (spine, hip and wrist)
Severe scoliosis
Extreme obesity or ascites
Vertebral deformities due to osteoarthritis or Scheuermann disease
Inadequate reference ranges
Inadequate operating procedures (e.g. calibration region selection, acquisition mode, positioning)

Modified from reference 32.

interest can be selected to exclude the joint. Some of these problems can be overcome with adequately trained staff and rigorous quality control.

4.3.5 **Reference ranges**

Normal reference ranges for BMD must be taken from appropriate populations. Small differences between ranges have a large impact on the numbers of patients with a BMD below a diagnostic threshold. For some populations, the use of appropriately derived reference ranges rather than those provided by the manufacturers is essential. All reference ranges should be based on samples of adequate size drawn randomly from representative populations. The International Osteoporosis Foundation recommends the use of the National Health and Nutrition Examination Survey (NHANES) data for women aged 20–29 years (17).

4.4 **Assessment of fracture risk**

4.4.1 **Dual-energy X-ray absorptiometry and quantitative ultrasound densitometry**

Osteoporosis is clinically significant as a predictor of fractures, and it is for this reason that BMD measurements are of such great interest. From this point of view, the importance of BMD measurements is not how closely they measure BMD or BMC, but their sensitivity and specificity in predicting future fractures. Many well-controlled prospective studies with DXA indicate that the age-adjusted relative increase in risk of fracture approximately doubles for each standard deviation decrease in BMD (see Table 11) (25).

Table 11
Age-adjusted relative increase in risk of fracture (with 95% confidence interval) in women for each standard deviation decrease in BMD (absorptiometry) below the age-adjusted mean

Site of measurement	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

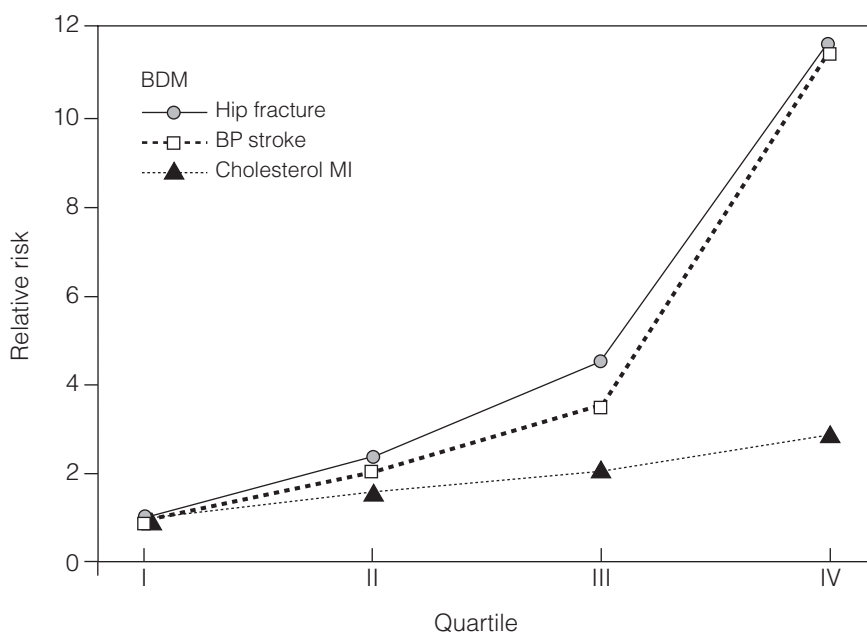
Modified from reference 25.

Average lifetime risks of common osteoporotic fractures in Caucasian men and women are approximately 13% and 40%, respectively, at age 50 years. These risks are nearly doubled in individuals with low bone mass and nearly 4-fold greater in women with osteoporosis (50% lifetime risk at age 50 years) compared to women with an average BMD (13% lifetime risk at age 50 years) (3). The risk can be doubled again when individuals have had a fragility fracture.

Estimating fracture risk from BMD measurements is comparable to assessing the risk of stroke from blood pressure readings. Blood pressure values are continuously distributed in the population, as is BMD. In the same way that a patient above a cut-off level for blood pressure is diagnosed as hypertensive, the diagnosis of osteoporosis is based on a value for BMD below a cut-off threshold, but there is no absolute threshold of BMD that discriminates absolutely between those who will or will not fracture. The performance of BMD in predicting fracture is, however, at least as good as that of blood pressure in predicting stroke, and considerably better than the use of serum cholesterol to predict coronary artery disease (14, 25, 33) (Figure 8). Nevertheless, it should be recognized that a normal BMD does not in itself guarantee that fracture will not occur, only that the risk is decreased. If, however, BMD is in the osteoporotic range, fractures are likely. The low detection rate is one of the reasons why widespread screening of population bases is not recommended for women at the time of the menopause (see section 6.5).

The gradient of risk depends on the technique used, the site measured and the fracture of interest. In general, site-specific measurements show the higher gradients of risk for their respective sites. For example, measurements at the hip predict hip fracture with greater power than do measurements at the heel, lumbar spine or forearm (25, 34). Gradients of risk range from 1.5 to 3.0 for each standard

Figure 8
Relative risk of clinical outcomes according to risk factors categorized by quartiles^a



WHO 03.162

Those in the lowest quartile are accorded a risk of 1.0. The 25% of the population with the lowest BMD has a greater than 10-fold increase in hip fracture risk. BMD measurements perform as well as measurements of blood pressure (BP) to predict stroke, and better than serum cholesterol to predict myocardial infarction (MI) in men.

^a Reproduced from reference 33 with the permission of Oxford University Press.

deviation decrease BMD (see Table 11). In this sense, the performance characteristics of ultrasound are similar. Most studies suggest that measurements of BUA or SOS are associated with a 1.5–2-fold increase in risk for each standard deviation decrease in BMD (5). Comparative studies indicate that these gradients of risk are very similar to those provided by peripheral assessment of BMD at appendicular sites by absorptiometric techniques to predict any osteoporotic fracture (23, 35).

Several studies suggest that ultrasound measures some aspects of skeletal status and fragility that cannot be measured using absorptiometric techniques alone. In the EPIDOS study, for example, the relative risk of hip fracture increased 1.9-fold for each standard deviation decrease in femoral BMD (8). A similar gradient of risk was observed for BUA (relative risk = 2.0) and for SOS (relative risk = 1.7). When these relative risks were adjusted for femoral BMD,

an effect of attenuation and speed of sound persisted (relative risks 1.7 and 1.4 respectively). This may be due to a component of risk uniquely detected by ultrasound measurement or merely a consequence of measurements at multiple sites by techniques with different sources of error. Indeed, measurement of BMD by absorptiometric techniques at more than one site improves the prediction of fractures (36).

Whether ultrasound adds a dimension of risk that would not also be obtained by an absorptiometric measurement at another site is a question which at present remains open (37). The choice of site for assessment will depend both on the reason for the assessment and on the age of the patient. For example, spinal osteoarthritis and osteoarthrosis are particularly common in the elderly, in whom this site is less suitable for diagnostic purposes. However, changes in the spine resulting from treatment of estrogen deficiency are often more marked and can be detected earlier than those at the hip or wrist. Since hip fracture is the major concern in the elderly, measurement at that site is preferable since such measurements predict hip fractures most accurately. Thus, measurements made at the wrist, heel, spine or hip may be useful in younger individuals, e.g. at the time of menopause (to assess the risk of future fractures) while those at the hip alone are useful in the elderly.

4.4.2 ***Radiographic assessment***

Although the “gold standard” for the diagnosis of osteoporosis is DXA, it can often be diagnosed from X-rays (38), which, in many regions of the world, will be the only tool available. A decrease in the apparent density of bone detected radiographically is not specific for osteoporosis and is more appropriately termed osteopenia. In addition to osteopenia, osteoporosis is associated with abnormalities in the trabecular architecture, a decrease in cortical width and visible evidence of past fractures. Fractures are prominent in the spine and, of the vertebral deformities on X-ray, approximately one-third will come to clinical attention (see section 1.3.2).

In postmenopausal osteoporosis, the numbers of trabeculae are decreased, and those remaining hypertrophy, particularly the vertebral trabeculae. The preferential loss of horizontal trabeculae gives rise to a striated appearance. These changes in trabecular markings differ from those observed in glucocorticoid-induced osteoporosis or in osteomalacia. In these disorders, trabecular markings usually become indistinct, giving rise to a fuzzy or ground glass appearance. In corticosteroid-induced osteoporosis, pseudo-callus may also be found in

the absence of overt vertebral deformities. It is important to recognize that vertebral deformities are not invariably due to osteoporosis. As mentioned earlier, other common causes include scoliosis, Scheuermann disease and osteoarthritis.

The proximal femur has a distinctive pattern of trabecular architecture which is disturbed in the course of osteoporosis. The pattern of loss provides a semiquantitative estimate of trabecular losses. At cortical bone sites, osteoporosis induces thinning of the cortex and an increase in cortical porosity, both of which may be visible on X-rays. A number of quantitative techniques have been developed for their assessment, including metacarpal radiogrammetry and radiographic absorptiometric techniques, and may be of value where other technologies are not available (38).

4.4.3 **Biochemical assessment of fracture risk**

Biochemical markers of bone turnover may be divided into two groups, namely markers of bone resorption and markers of bone formation (39). The principal markers of bone formation are total alkaline phosphatase, the bone isoenzyme of alkaline phosphatase, osteocalcin, and the procollagen propeptides of type I collagen. The most widely used markers of bone resorption are hydroxyproline, pyridinium cross-links, and their peptides. Tartrate-resistant acid phosphatase and hydroxylysine glycosides are less commonly used. Fasting urinary calcium excretion (calcium/creatinine ratio) provides a net index of the balance between bone resorption and formation.

While breakdown markers may change within 1 or 2 months of starting a bone treatment, several months of treatment are required before any significant change in formation markers becomes apparent. Since BMD changes even more slowly, the rapid changes in markers induced by treatment may be useful in monitoring treatment. Their measurement has provided valuable insights into the pharmacodynamics of bone treatments, but their use in monitoring individuals requires further study because of their precision errors and biological variation.

Several studies with these markers have found sustained increases in bone turnover in late postmenopausal and elderly women, which appear to be triggered by the menopause. These changes are insufficiently discriminatory, however, to provide a diagnostic test for osteoporosis.

Biochemical indices of skeletal metabolism are of greatest value in assessing fracture risk. Prospective studies have shown an association of osteoporotic fracture with indices of bone turnover, independent of bone density, in women at the time of the menopause (40, 41) and in elderly women (42). In the latter, when values for resorption markers exceed the reference range for premenopausal women, the risk of hip fracture is increased approximately 2-fold. An increase in risk persists even after adjusting for BMD. These studies suggest that combining BMD measurements with indices of bone turnover may improve fracture prediction.

4.4.4 **Clinical risk factors**

Many risk factors for osteoporosis have been identified (Table 3; see also sections 2 and 3). In general, the specificity and sensitivity of risk factor scores in predicting either BMD, or fracture risk are relatively poor (43–46), partly because common but relatively weak risk factors, such as cigarette smoking and physical inactivity, have a much greater influence on such scores than relatively uncommon but strong risk factors such as previous glucocorticoid therapy and hypogonadism. Risk factors for falling, such as visual impairment, reduced mobility and treatment with sedatives, are more strongly predictive of fracture in the elderly than in younger individuals (47).

Hypogonadism is an important risk factor for osteoporosis in both sexes. In young women, it may be primary or secondary to conditions such as anorexia nervosa, exercise-induced amenorrhoea, chronic illness, hyperprolactinaemia and gynaecological disorders. Premature menopause, whether spontaneous or the result of surgery, chemotherapy or radiotherapy, also increases the risk of osteoporosis. In men, hypogonadism may be caused, inter alia, by Klinefelter syndrome, hypopituitarism, hyperprolactinaemia and castration, e.g. after prostatic surgery.

As shown in Table 12, glucocorticoids are a risk factor for osteoporosis. They are widely used for the treatment of a number of conditions, including rheumatic disorders, asthma and other lung conditions, inflammatory bowel disease, skin disorders, and vasculitic syndromes. Bone loss is believed to be most rapid during the first few months of treatment; it affects both the axial and appendicular skeleton, but is most marked in the spine, where cancellous bone predominates. It occurs with both parenteral and oral glucocorticoid therapy, but with inhaled glucocorticoid therapy is less well documented. However, high doses of inhaled glucocorticoids may have adverse skeletal effects. Although the skeletal response to glucocorticoids varies, high

Table 12
Risk factors for osteoporosis

Endogenous	Exogenous
Female sex	Premature menopause
Age	Primary or secondary amenorrhoea
Slight body build	Primary and secondary hypogonadism in men
Asian or Caucasian race	Previous fragility fracture
	Glucocorticoid therapy
	Maternal history of hip fracture
	Low body weight
	Cigarette smoking
	Excessive alcohol consumption
	Prolonged immobilization
	Low dietary calcium intake
	Vitamin D deficiency

doses are generally associated with greater adverse skeletal effects. Daily doses of prednisolone below 7.5mg are less likely to result in increased rates of bone loss and fracture (48).

As previously mentioned (see section 3.5.3), a history of fragility fracture is an important independent risk factor for further fracture. For example, the presence of two or more prevalent vertebral fractures was associated with a 12-fold increase in fracture risk for any given BMD (25), and women with a past history of non-vertebral fractures were found to have a 3-fold increase in the risk of subsequent spine fractures (34).

Case–control studies of hip fractures in both men and women have shown that, with disorders associated with secondary osteoporosis, such as previous hyperthyroidism, gastric surgery and hypogonadism, the risk of fracture is increased (43, 49–51). The risk also increased with conditions causing an increased risk of falling, such as hemiparesis, Parkinson disease, dementia, vertigo, alcoholism and blindness (49). A prospective study in Australia showed a higher risk of hip fracture with low bone density, quadriceps weakness, increased body sway, falls in the previous year and previous fractures (52).

Of the endogenous and exogenous risk factors shown in Table 12, smoking, excessive alcohol consumption and low dietary calcium intake are relatively weak risks. Complete immobility leads to rapid bone loss at the sites concerned but the effects of lesser degrees of physical inactivity on the risk of osteoporosis are less well documented. Low BMI is an important risk factor for both osteoporosis and fractures, probably because of its association with bone size.

Finally, a parental history of hip fracture is an independent risk factor for fracture. For any given BMD, the risk of hip fracture is increased approximately 2-fold (44).

The value of identifying risk factors to target treatment is discussed in section 4.5.3.

4.5 **Assessment of osteoporosis**

4.5.1 **Diagnostic work up**

The same diagnostic approach would be adopted in all patients with osteoporosis irrespective of the presence or absence of fragility fractures. The range of clinical and biological tests used to assess osteoporosis will depend on the severity of the disease, the age at presentation, the presence or absence of vertebral fractures, and the reason for the assessment, which may be to:

- exclude a disease which can mimic osteoporosis;
- elucidate the causes of osteoporosis and the contributory factors (see Tables 5 and 6);
- assess the severity of osteoporosis and thus to determine the risk of subsequent fractures;
- select the most appropriate treatment;
- establish baseline measurements for subsequent monitoring of treatment.

Table 13 lists the diagnostic procedures used to investigate osteoporosis. These may be used to:

- establish the diagnosis of osteoporosis (e.g. DXA or X-rays);
- establish the cause (e.g. thyroid function tests for hyperthyroidism, and urinary free cortisol for Cushing syndrome);
- establish the differential diagnosis (e.g. protein electrophoresis for myeloma, and serum calcium and alkaline phosphatase for osteomalacia).

Investigations commonly carried out in specialized centres include determination of the biochemical indices of bone turnover, serum

Table 13
Diagnostic procedures used to investigate osteoporosis

History and physical examination
Laboratory findings: blood cell count, measurement of sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase, liver transaminases
Lateral radiography of lumbar and thoracic spinal column
Bone densitometry (DXA or SXA)
Sex hormones (particularly in men)

PTH, and serum $1\alpha,25$ -dihydroxycholecalciferol, serum or urine protein electrophoresis, measurement of fasting and 24-hour urinary calcium, and urinary free cortisol, and thyroid function tests and transiliac bone biopsy.

4.5.2 **Differential diagnosis**

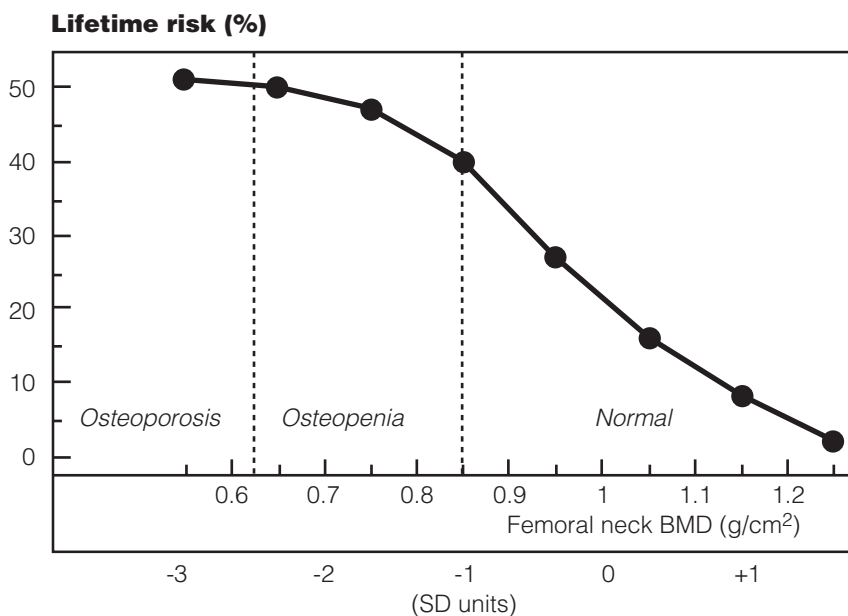
Underlying causes of bone loss are more commonly found in men than in women. In over 50% of men presenting with symptomatic vertebral crush fractures, an underlying cause of osteoporosis, such as hypogonadism, oral steroid therapy and alcohol dependence, is identified (53, 54). A significantly increased risk of vertebral fractures was found to be associated with smoking, alcohol consumption and underlying causes of osteoporosis (55). A recent case-control study in men in Newcastle upon Tyne, England, showed an increased risk of vertebral fractures with oral steroid therapy, anticonvulsant treatment, smoking, alcohol dependence and hypogonadism (56). For hip fractures, however, the risk factors in men are similar to those in women (49, 51).

Both osteomalacia and malignancy commonly induce bone loss and fractures. Osteomalacia is characterized by a defect of mineralization of bone matrix most commonly due to impaired intake, production or metabolism of vitamin D. Other causes include impaired phosphate transport, the chronic use of some drugs such as aluminium salts, other phosphate-binding antacids and anticonvulsants, and high doses of fluoride or etidronate. In most cases, osteomalacia is suspected based on the clinical history and biochemical abnormalities, such as low values of serum and urinary calcium, serum phosphate and $1\alpha,25$ -dihydroxycholecalciferol, and high values of alkaline phosphatase and PTH. A transiliac bone biopsy after tetracycline labelling can unequivocally demonstrate defects in mineralization.

Diffuse osteoporosis with or without pathological fractures is common in patients with multiple myeloma, a condition characterized by severe bone pain, increased sedimentation rate, and Bence Jones proteinuria. The diagnosis can be confirmed by bone marrow aspiration, and serum and urine protein electrophoresis. Similarly, pathological fractures due to metastatic malignancies can mimic osteoporosis but can be excluded by clinical and radiological examination, biological tests, e.g. for tumour markers, and scintigraphy or other imaging techniques. Finally, vertebral fractures in osteoporosis should be differentiated from vertebral deformities due to other disorders such as scoliosis, osteoarthritis and Scheuermann disease.

Figure 9

Remaining lifetime risk of hip fracture in women at age 50 years based on BMD at the femoral neck



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4.5.3 Identification of cases for treatment

No universally accepted policy exists at present on screening to identify patients at high risk of fracture. The test used to diagnose osteoporosis, bone densitometry, has high specificity but low sensitivity. Thus, the risk of fracture is very high when osteoporosis is present, but by no means negligible when BMD is normal (Figure 9). In the absence of a generally accepted screening policy, a case-finding strategy can identify people with fragility fractures or other strong risk factors for fracture. The use of risk factors that add information on fracture risk independently of BMD will improve the predictive value of the assessment (23, 40, 42, 44, 57).

Examples of risk factors for hip fracture in women that are independent of BMD (Table 14) include a high biochemical index of bone resorption (prospective studies suggest an approximately 2-fold increase in fracture risk in women, independently of BMD) (40, 42), low body weight or low BMI (44, 58), prior osteoporotic fracture (42, 59, 60), a family history of fragility fracture, and cigarette smoking (43). Some of these have been incorporated into practice guidelines (32, 61, 62). Some studies suggest that the geometry of the hip is also a BMD-independent risk factor for hip fracture. The risk increases

Table 14
Examples of significant relative risks of hip fracture in women with and without adjustment for BMD

Risk factor	Relative risk	
	Crude	Adjusted for BMD
Hip BMD 1 SD (standard deviation) below mean population value	2.6	
Non-carboxylated osteocalcin above normal range	2.0	1.8
Biochemical index of bone resorption (CTX) above premenopausal range	2.2	2.0
Prior fragility fracture after age 50 years	1.4	1.3
Body weight below 57.8kg	1.8	1.4
First-degree relative with a history of fragility fractures and aged 50 years or over	1.7	1.5
Maternal family history of hip fracture	2.0	1.9
Current cigarette smoking	1.9	1.2
Poor visual acuity (<2/10)	2.0	2.0
Low gait speed (1 SD decrease)	1.4	1.3
Increase in body sway (1 SD increase)	1.9	1.7

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approximately 2-fold in women with the length of the femoral neck (63) after adjustment for BMD, but may be a measurement artifact (64). Density-independent components of fracture risk, such as falls and postural instability, are clearly important for hip fracture. A variety of simple tests have been devised to detect postural instability and poor visual acuity, both of which have been shown to be associated with increased risk of hip fracture independently of BMD (51, 59). Some care is required in the use of density-independent risk factors to identify individuals for pharmacological interventions that affect skeletal metabolism since, e.g. inhibitors of bone turnover may not be effective in populations selected on the basis of falling. With this proviso, any of these risk factors may be used to increase the value of BMD in predicting fractures. For example, an individual with a BMD 1 standard deviation below the population average and poor visual acuity would have a relative risk of approximately 3 ($2.6 \times 2.0 \times$ adjustment factor).

The reason why the true relative risk is not a multiple of the risks given in Table 14 relates to the need to adjust risks to population risks. In the example given above, poor visual acuity was associated with a relative risk of 2.0 compared to individuals with better acuity.

Table 15
Estimates of population relative risks derived from relative risks in epidemiological studies (RR cases versus controls) according to the prevalence of risk factors in the population

Prevalence of risk factor (%)	RR			
	1.5	2.0	2.5	3.0
5	1.46	1.90	2.33	2.73
10	1.43	1.82	2.17	2.50
20	1.37	1.67	1.92	2.14
30	1.30	1.54	1.72	1.88
50	1.20	1.33	1.43	1.50

Poor visual acuity was found in 7.3% of the population. The relative risk adjusted for the population is approximately:

$$RR / (p \times RR + (1- p))$$

Where *p* is the prevalence of the risk factor and RR the unadjusted value of the relative risk. In the example given above, the relative risk with poor visual acuity adjusted to the general population is:

$$2.0 / (0.073 \times 2.0 + (1 - 0.073)) = 1.86$$

Further examples of the adjustments required are provided in Table 15. The stronger the risk factor and the higher the prevalence, the larger the adjustment.

Downward adjustment of the risk factor associated with a low BMD is also required (57, 65). Hip fracture rates increase logarithmically with decreasing BMD, but BMD is normally distributed. For this reason, individuals with a BMD equal to the mean have a risk of hip fracture that is lower than the average risk. On the assumption that the risk increases 2.6-fold for each standard deviation decrease in BMD, the risk of hip fracture of an individual with a T-score of -1 would be 1.65 (57). Thus, in the individual with poor visual acuity and a BMD 1 standard deviation below the population average, the relative risk of hip fracture is 1.65 × 1.86 = 3.0.

The examples given in Table 14 of risk estimates adjusted for BMD are not otherwise adjusted. For example, the increase in risk associated with low body weight is not adjusted for postural instability. It will be necessary to make such adjustments from several large population studies before these can be used as independent and additive risk functions.

The multiple factors that contribute to fracture risk more or less independently suggest that the gradient of risk between those characterized as high or low risk can be increased by multiple assessments that contribute to risk independently. The use of multiple risk factors increases the sensitivity of assessment substantially without any decrease in specificity (57). The assessment of absolute risk is more useful than that of relative risk in deciding the intervention threshold for an individual. Absolute risk depends on age and life expectancy as well as current relative risk. For example, the lifetime risk of hip fracture in a Swedish woman at age 50 years with osteoporosis would be approximately 43%, but the remaining lifetime risk of an osteoporotic fracture at 85 years would be 19%.

In the case of hip fracture, average lifetime risks remain relatively constant with age. Although the absolute risk of hip fracture increases with age, so too does mortality and the two factors tend to cancel each other out. For Swedish women at age 50 years, the lifetime risk of hip fracture is 22.7% and decreases with age, but remains relatively high at 19% at age 85 years. Average lifetime risks for men are approximately half those for women (9.6–11%) due to the lower absolute risk and lower life expectancy. The effect of increases in relative risk on lifetime risks is shown in Table 16 for Swedish women and men (57). As would be expected, lifetime risk increases with relative risk at all ages for both sexes.

Further examples are provided by the interaction of biochemical markers of skeletal turnover and BMD. The EPIDOS (Epidémiologie de l'Ostéoporose [epidemiology of osteoporosis]) study has shown that BMD and urinary C-terminal cross-link peptide of collagen (CTX) contribute independently to hip fracture risk in women at age 81 years (66), when the average lifetime risk of hip fracture is 21%. In women with osteoporosis, the lifetime risk for hip fractures rises to 32% at this age, while in those with values of urinary CTX above the premenopausal range the lifetime risk is 34%. As would be expected, combining risk factors has a marked effect, and the combination of low hip BMD and high CTX gives a lifetime risk of fracture of 45%. Similarly, combining high CTX with a history of fracture has a lifetime risk of 52% at age 81 years (67). These data show the value of adding risk factors together and thus obtaining lifetime risks of fracture that exceed intervention thresholds.

The predictive value of BMD and other risk factors over a lifetime is unknown. In the case of BMD there is reasonable evidence to suggest that risks of fracture assessed in the short term overestimate such risks in the long term (65). For this reason, 10-year risks are more

Table 16
Lifetime risk of hip fracture in men and women in Sweden according to relative risk (RR) at the ages shown^a

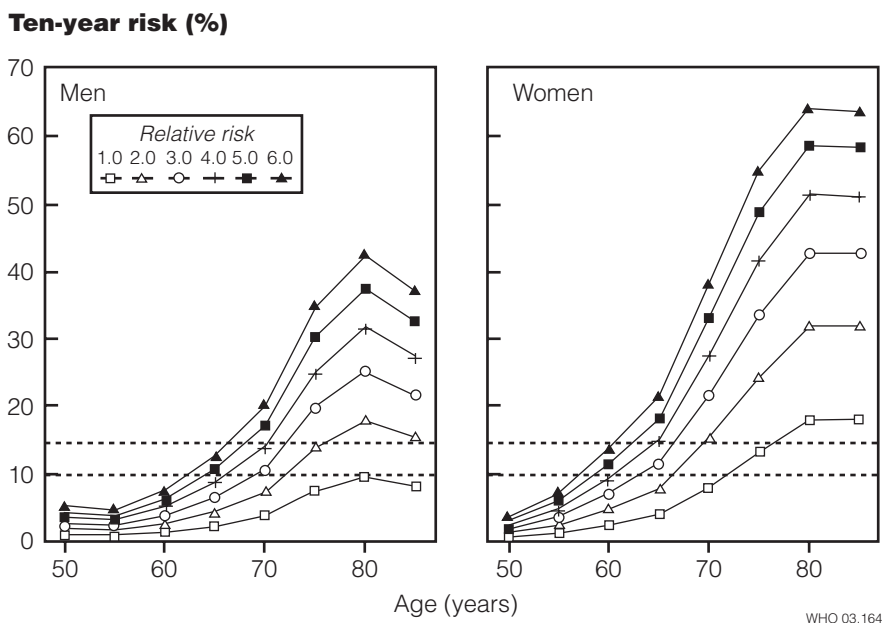
Relative risk	Age (years)							
	50	55	60	65	70	75	80	85
<i>Women</i>								
1.0	22.7	22.3	21.9	21.5	21.2	20.9	20.0	18.9
1.5	30.9	30.3	29.9	29.4	29.1	28.7	27.6	26.3
2.0	37.6	37.0	36.5	36.0	35.6	35.3	34.0	32.6
2.5	43.2	42.5	42.0	41.5	41.1	40.8	39.5	38.1
3.0	47.9	47.2	46.6	46.1	45.8	45.5	44.2	42.8
3.5	51.8	51.1	50.6	50.1	49.8	49.6	48.3	47.0
4.0	55.2	54.5	54.0	53.5	53.3	53.1	51.9	50.6
5.0	60.7	60.0	59.6	59.1	59.0	58.9	57.7	56.7
6.0	64.9	64.3	63.9	63.5	63.5	63.5	62.4	61.5
<i>Men</i>								
1.0	11.1	10.6	10.1	9.8	9.6	9.6	10.1	10.7
1.5	15.7	14.9	14.4	13.9	13.6	13.7	14.4	15.3
2.0	19.8	18.9	18.2	17.7	17.3	17.4	18.2	19.4
2.5	23.4	22.4	21.6	21.0	20.6	20.7	21.8	23.1
3.0	26.7	25.6	24.7	24.1	23.6	23.8	25.0	26.5
3.5	29.7	28.5	27.6	26.9	26.4	26.6	27.9	29.6
4.0	32.4	31.1	30.2	29.5	29.0	29.2	30.6	32.5
5.0	37.2	35.8	34.8	34.0	33.5	33.8	35.4	37.6
6.0	41.3	39.8	38.7	38.0	37.4	37.8	39.6	42.0

^a Lifetime risk at any age is determined from the competing probabilities of death or hip fracture. Modified from reference 57.

accurate, and also take account of the fact that many treatments are given only for a few years (up to 5 years) because of the slow attenuation of effect after stopping treatment, e.g. when bisphosphonates and HRT are used (68). The International Osteoporosis Foundation has recently recommended that assessments of the risk of fracture should be expressed as absolute 10-year risks (17), particularly when technologies other than DXA, where the T-score is misleading, are used.

Evaluating fracture risk accurately is essential if interventions are to be targeted only to those at highest risk. The choice of a cut-off value for relative risk or 10-year probability that provides an intervention threshold will depend on clinical practice, the effectiveness of treatment (compliance, continuance and efficacy), the type of fracture expected as well as the costs of treatment and of fractures. For hip fractures, interventions are reasonable in terms of cost–utility where the 10-year probability of hip fracture exceeds 10–15%. Ten-year

Figure 10
Ten-year probability of hip fracture in Swedish men and women according to population relative risks^a



The horizontal dotted lines denote the probability at which interventions are cost-effective.

^a Based on data from reference 57.

probabilities of hip fracture according to population relative risks are shown in Figure 10 for men and women in Sweden (57). The 10-year probability of 10–15% is exceeded in Swedish women aged 80 years and over. For individuals with a population relative risk of 2.0, the threshold is exceeded at 70 years, so that the higher the relative risk, the younger the age that interventions aimed at preventing hip fracture are cost-effective.

In addition, hip fracture is only one possible outcome, so that intervention thresholds also depend on the probability of other osteoporotic fractures. Several groups in Europe and the USA have drawn up evidence-based practice guidelines in which intervention thresholds are based on economic analyses (32, 61, 62, 69). While there are major differences between these guidelines (70), for most interventions envisaged, they agree that individuals with osteoporosis should be offered treatment, and that this can be justified from a health economics perspective. This corresponds to a relative risk of approximately 3.0 in women within 10 years of the menopause when

adjusted to the risk of the general population. A combination of risk factors yielding a high relative risk exceeding this threshold of risk is an indication for intervention. For example, combining the fracture risk associated with menopause below age 50 years and a prior fragility fracture gives a relative risk of 2.7, so that the threshold would be exceeded by the addition of any further risk factor with a relative risk exceeding 1.1 (e.g. smoking or low body weight). In this example, therefore, combining risk factors without measuring BMD indicates when intervention is necessary. The same combination of risk factors and BMD or ultrasound values in the lower half of the reference range would also exceed this threshold.

The above notwithstanding, the assessment of BMD provides the most sensitive and specific assessment of osteoporosis available to date and forms the cornerstone of case-finding strategies. Treatment is justified in patients with low BMD in the presence of relatively weak risk factors.

Risk factors providing indications for bone mineral densitometry are given in Table 17, which is based on published guidelines (32, 62). Patients with the risk factors listed have BMD values lower than that of the general community and where “osteoporosis is confirmed” the risk of fracture is high. Although this strategy does not benefit all individuals at high risk and is therefore conservative, it can be justified from the perspective of health economics.

These indications for bone densitometry do not mean that all patients with such risk factors require diagnostic assessment. For example, patients with more than one fragility fracture should be offered treatment irrespective of their BMD, but the latter may be required in the monitoring of treatment.

4.5.4 ***National guidelines***

National strategies for the assessment and diagnosis of osteoporosis will depend on many considerations, but the size of the problem expressed both in absolute terms and relative to other health care needs is of greatest importance. In many Western countries the likelihood that any individual will suffer an osteoporotic fracture is relatively high. The estimated lifetime risk of a hip fracture in Caucasian women in the United Kingdom and the USA at menopause ranges from 14 to 23% (71, 72). The risk of other common types of osteoporotic fractures is nearly as high (73), so that the combined fracture risk is 30–45% (16, 72). Thus, more than one-third of adult women in the United Kingdom will sustain one or more osteoporotic fractures during their lifetime. This estimate is conservative because it

Table 17

Risk factors providing indications for diagnostic use of bone mineral densitometry

-
1. Strong risk factors:
 - Estrogen status:
 - Premature menopause (<45 years)
 - Prolonged secondary amenorrhoea (>1 year)
 - Primary hypogonadism
 - Corticosteroid therapy — prednisolone (or equivalent) 7.5mg/day or more with an expected use of more than 6 months
 - Maternal family history of hip fracture
 - Low body mass index (<19kg/m²)
 - Other disorders associated with osteoporosis:
 - Anorexia nervosa
 - Malabsorption syndromes, including chronic liver disease, and inflammatory bowel disease
 - Primary hyperparathyroidism
 - Post-transplantation
 - Chronic renal failure
 - Hyperthyroidism
 - Prolonged immobilization
 - Cushing syndrome
 2. Radiographic evidence of osteopenia and/or vertebral deformity
 3. Previous fragility fracture, particularly of the spine or wrist
 4. Loss of height, thoracic kyphosis (after radiographic confirmation of vertebral deformities)
-

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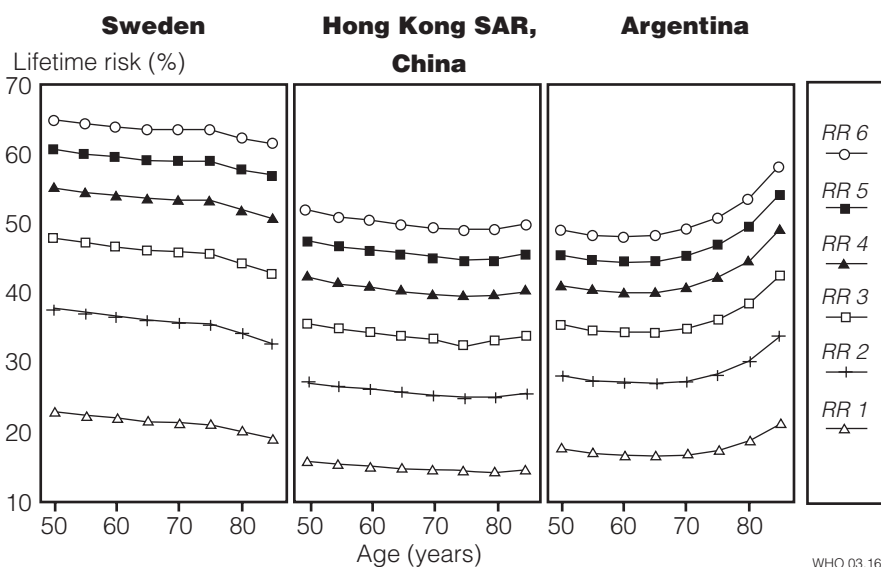
does not include fractures at other sites and only takes into account those vertebral fractures which come to clinical attention, so that the true risk of fracture must be higher. In addition, not all estimates take into account the steady increase in life expectancy (74).

The risk of fracture varies, however, in different regions of the world (see section 3.3). Even within Europe, the risk of hip fracture varies more than 10-fold among countries (75, 76), and variation in the rate of hospitalization for vertebral fracture is comparable (77). The lowest prevalence of hip fracture is found in developing countries, in part because of the lower risk but also because of lower life expectancy. A caveat is that countries need to take into account the priority that osteoporosis has over other health care needs. In addition, the size of the burden of osteoporosis in a particular country cannot be deduced merely from a knowledge of the demography of that country.

The frequency of osteoporotic fracture is increasing worldwide. In many countries, the age- and sex-specific risks of fracture have increased (see section 3.4). There is some evidence that this trend has

Figure 11

Remaining lifetime risk of hip fractures^a in women aged 50 years or more from Argentina, Hong Kong SAR, and Sweden, according to relative risk



The horizontal dotted line indicates a lifetime risk of 40% and corresponds to a relative risk of 2.2 in Swedish women aged 50 years, but a relative risk of 4.1 and 3.8 in women of the same age from Argentina and Hong Kong SAR, respectively.

^a Based on data from references 74 (Sweden), 79 (Argentina) and 78 (Hong Kong SAR). Life expectancy is based on unpublished WHO figures for 1995.

levelled off, at least for hip fracture rates in some Western countries, but the number of fractures will increase because of the marked increase in the elderly population everywhere, but particularly in Asia (78). However, case-finding strategies need to be tailored to the size of the current problem of fragility fractures. The absolute risk of fractures will depend on estimates of current risk and future mortality. Examples of lifetime risk in different countries are shown in Figure 11 according to the relative risk of the individual. Thus, a Swedish woman aged 70 years with a relative risk of hip fracture of 4.0 might be considered to require treatment whereas the same absolute risk in a woman in the Hong Kong Special Administrative Region (SAR) of China would require more or stronger risk factors than a woman in Stockholm to require treatment using the same threshold. Each country will therefore need to develop its own case-finding strategies until such time as international guidelines can be drawn up that cater for the variation in risks between countries.

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5. Prevention and treatment

5.1 Introduction

A large number of bone-active agents have been used to treat osteoporosis, and patterns of use vary greatly from country to country. For example, fluoride is widely used in Germany, but is not licensed for use in the United Kingdom or the USA. Calcitonin is available in many countries, but is used mainly in Japan and the USA. The wide differences in prescribing practices pose problems in describing the treatment of osteoporosis in a manner appropriate for all countries. Moreover, few comparative studies of different treatments have been conducted so that it is difficult to decide which are the most effective. The choice of agent will depend not only on effectiveness but also on other considerations such as side-effects, cost and availability.

In the management of many diseases, the strategies used are classified as primary, secondary or tertiary prevention, depending on the extent to which the individual being treated already manifests the condition. In this context, the aims of intervention are to prevent bone loss in individuals at risk of osteoporosis or in patients with osteoporosis. Treatments may be aimed at maintaining bone mass or rectifying skeletal deficits and architectural abnormalities, though in practice the latter remains experimental. The objectives are the same — to reduce the incidence of osteoporotic fractures. Interventions may be directed at specific populations e.g. postmenopausal women, men, and people with osteoporosis due to secondary causes. All these distinctions are somewhat artificial for a number of reasons. First, loss of bone mass is almost universal in older people, and about 50% of postmenopausal women will eventually sustain a fracture of some kind. Many vertebral fractures are asymptomatic, and the definition of a vertebral fracture remains the subject of controversy. The distinction between those who already manifest the condition (i.e. have fractures) and those who are at risk, therefore becomes blurred. Second, osteoporosis is defined operationally by BMD, which again blurs the distinction between those with the clinical consequences of osteoporosis and those merely at risk, since diagnostic thresholds derived from continuous variables are arbitrary. Third, the difference between prevention and treatment is difficult to define because the same interventions are used for both purposes. For example, an early postmenopausal woman who also has already had several fractures will be given the same advice on exercise, calcium intake and smoking cessation, and may be offered similar drugs. Nevertheless, some agents may be more suitable for younger women at the menopause,

whereas others may be more suitable for the elderly. For these reasons, the prevention and treatment of osteoporosis are discussed together in this section.

The choice of intervention and the cost-effectiveness of any management strategy will be determined partly by the absolute fracture risk. Thus, younger people in whom short-term fracture risk is low are probably best served by the recommendations on lifestyle outlined below, whereas pharmacological interventions are indicated in those at higher risk. The management of osteoporosis is intended to prevent either the first or any subsequent fracture by maximizing skeletal strength and/or minimizing skeletal trauma (see section 2.5). Changes in lifestyle, e.g. in nutrition, exercise and avoidance of immobility, are helpful, but individuals at high fracture risk will often also require pharmacological interventions. Possible methods of achieving these goals are reviewed in this section.

5.2 Non-pharmacological interventions

Skeletal strength in later life, when fracture risk is highest, is determined by the accrual of skeletal mass during childhood and adolescence, the extent to which peak bone mass is maintained during young adulthood, and the amount of bone lost in later life. Because these processes differ in each of these periods, and because it is theoretically possible that lifestyle factors may vary in importance from one period to another, the role of various lifestyle interventions should be assessed for each period. Thus lifestyle interventions directed at children will be delivered in quite a different way from those directed at adults. Nevertheless, all non-pharmacological interventions throughout the lifespan will have something in common. Attention has been focused on the role of diet (particularly calcium intake), exercise (as an anabolic stimulus and to optimize skeletal load-bearing efficiency), the maintenance of body weight, the timely onset of puberty, the maintenance of sex hormone production during adulthood, and the avoidance of skeletal insults (e.g. smoking, high alcohol intake, glucocorticoid drugs, etc.). Many of these are relevant at all ages (e.g. calcium intake and exercise), whereas others tend to be more important at particular stages of the life-cycle.

5.2.1 Diet

Calcium

Calcium is absorbed in the duodenum by an active mechanism regulated by $1\alpha,25$ -dihydroxycholecalciferol, and also passively in the more distal bowel. The efficiency of absorption declines with age. The

Table 18
Calcium content of some common foods

Food	Calcium content (mg/100g)	Calcium per serving (mg)
Whole milk:		
Cow	120	280
Goat	150	360
Skim milk	130	300
Yoghurt	130	260
Ice cream	140	100
Cheese:		
Hard	600–1000	150–250
Soft	300–400	80–100
Cottage cheese	60	15
Broccoli, cabbage	80	80
Cauliflower, lettuce	20	10
Small fish (e.g. sardines, including bones)	460	280
Nuts (cashews/almonds)	40–250	260
Tofu	105	
Bread:		
European	30–40	10
Arabic	60–90	15–20
Vine leaves	390	18
Rice	9	96
Semolina	48	
Seeds		
Sesame	1200	
Watermelon	50	
Pine	14	

calcium content of some common foods is shown in Table 18. In addition, in some areas, water (including some bottled mineral waters) may supply several hundred mg of calcium per litre.

Childhood and adolescence. If calcium intake during childhood and adolescence was a limiting factor for bone accrual, optimization of intake could have a substantial impact on peak bone density and the subsequent risk of osteoporotic fractures in old age. In a number of cross-sectional studies, the effects of dietary calcium intake on the bone density of young subjects has been assessed. These have often found that bone density is weakly related to calcium intake, but the relationship is not consistently statistically significant (1–3). There have also been studies on the effect of calcium supplementation on bone accrual in the young. Retrospective studies in which the bone density of older individuals has been assessed in relation to their

recalled calcium intake earlier in their lives have fairly consistently shown positive correlations between calcium intake earlier in life and adult bone density (4–6).

Giving calcium supplements to neonates, children and adolescents produces statistically significant increases in bone density (7–11), but these increases are generally of the order of only 1% of baseline bone density, and are consistent with the calcium supplement causing a reduction in bone remodelling space rather than a sustained increment in bone accretion. Thus of four studies in children followed up after stopping calcium supplementation, none showed any residual effect of the supplements, suggesting that the initially observed benefit was a remodelling transient (12–15). In contrast, one study did show some persisting benefit after the conclusion of a 1-year food-based intervention (7). Determining the extent to which such transients contributed to the results of the other studies will require larger studies of longer duration, extending from childhood to early adult life.

The baseline calcium intake is also important in assessing the response to calcium. Sustained beneficial effects are more likely to occur in subjects with low calcium intakes (7). Thus, the widespread use of calcium supplementation in young people consuming a balanced Western diet is hard to justify at present. In those with very low calcium intakes, either by choice or because of intolerance of dairy products, dietary modification or calcium supplementation is advisable.

Adults. There is some evidence that calcium supplementation in young women before the menopause is beneficial, but most research on the effects of calcium intake on bone has been in postmenopausal subjects. The considerable, but often contradictory observational data can now be replaced by the increasing amount of data from more than 20 randomized controlled trials, most of which have recently been reviewed and tabulated (16). Almost all of these studies show a small increase in BMD (~1%) in calcium-treated subjects. In the great majority of these studies, this increase is statistically significant at one or more skeletal sites (e.g. the forearm, spine, proximal femur or total body). The benefits appear to be more marked in late postmenopausal life than at the perimenopause (17), although some studies have found beneficial effects in this latter group also (18). The greater variation in rates of bone loss in perimenopausal women may obscure the relatively small effect of calcium supplementation. Some studies have reported that such effects are greater in those on lower calcium intakes (17).

A number of studies have suggested that the beneficial effect of calcium supplements is most marked in the first year of treatment, particularly at the sites where cancellous bone predominates (19). This effect is probably the result of a fall in circulating PTH concentrations, which decreases the number of bone remodelling units on the surface of cancellous bone. However, there is also a smaller residual positive effect on BMD of about 0.25% per year after the first year (19). If this were to continue over 30 years of postmenopausal life, a cumulative benefit of 7.5% would be expected, which would reduce fracture risk by about one-third. Furthermore, three studies have found a significant effect of calcium monotherapy on fracture incidence despite observed between-group differences in bone density of <2% (19–21). However, when all randomized clinical trials reporting fractures are meta-analysed, calcium supplementation is associated with a relative risk (RR) of vertebral fracture of 0.77 (95% confidence interval [CI] 0.54–1.09) and a relative risk of non-vertebral fracture of 0.86 (95% CI 0.43–1.72) (22). A large, international case–control study found that hip fractures were less frequent in those receiving calcium supplements (RR 0.75, 95% CI 0.60–0.94) (23).

Based on this evidence, a number of agencies have adopted recommendations for dietary calcium intake throughout life (see Table 19). These vary widely from country to country, reflecting some of the scientific uncertainties (24). The fractional absorption of calcium from dairy products is higher than that from vegetables, and cheese may be marginally superior to milk in this respect (25).

Table 19
Recommended dietary calcium intakes

Recommending Body	Population	Age (years)	Intake (mg/day)
Institute of Medicine (USA): Adequate intake for calcium (1997)		0–0.5	210
		0.5–1.0	270
		1–3	500
		4–8	800
		9–13	1300
		14–18	1300
		19–30	1000
		31–50	1000
		51–70	1200
		>70	1200
	Pregnant females	18	1300
		19–50	1000
	Lactating females	18	1300
		19–50	1000

Table 19 (continued)
Recommended dietary calcium intakes

Recommending Body	Population	Age (years)	Intake (mg/day)
European Community		6–11 months	400
		1–3 years	400
		4–6	450
		7–10	550
	Male adolescents	11–17	1000
	Female adolescents	11–17	800
	Adults (both sexes)	PRI	700
		AR	550
		LTI	400
	Pregnant females		700
	Lactating females		1200
National Institute of Health (USA): optimal calcium intake (1994)	Infants	0–0.5	400
		0.5–1.0	600
	Children	1–5	800
		6–10	800–1200
		11–24	1200–1500
	Males	25–65	1000
		>65	1500
		11–24	1200–1500
		25–50	1000
		50–65	1500
	Females	>65	1500
		50–65	1000
		Pregnant females	1200
		Lactating females	1200
	Females using estrogen	50–65	1000
Nordic nutrition recommendations (1996)	Infants	0–0.5	360
		0.5–1.0	540
	Children	1–3	600
		4–6	600
		7–10	700
		11–20	900
	Males	20–60	800
		>60	800
		11–20	900
		20–60	800
	Females	>60 ^a	800
		Pregnant females	900
		Lactating females	1200

PRI, Population reference intake (intake sufficient for practically all healthy people in a population); AR, average requirements; LTI, lowest threshold limit (intake below which, based on current knowledge, almost all individuals will be unlikely to maintain metabolic integrity according to criterion chosen).

^a Supplementation with 500–1000mg/day may delay bone loss.

Calcium supplements are generally well tolerated and reports of significant side-effects are rare (26), but some individuals complain of constipation when taking them. The possibility that high calcium intakes might lead to urinary calculi in susceptible subjects was a cause for concern, and it was found in an observational study that whereas dietary calcium intake was inversely related to the risk of stone formation, the use of calcium supplements increased this risk by 20% (27). This apparent inconsistency may arise from the reduction in intestinal oxalate absorption that occurs when calcium is taken with meals. It has been suggested that high calcium intakes are associated with a reduced risk of colorectal cancer (28), reduced blood pressure (29) and reduced serum lipid concentrations (30), but these associations require further investigation.

Vitamin D

Vitamin D₃, or cholecalciferol, is produced in the skin as a result of the action of ultraviolet light on 7-dehydrocholesterol. The efficiency of this conversion is reduced with age, skin pigmentation, and potentially with the extensive use of sunscreens applied on the skin. Where foods are not fortified, the diet is relatively unimportant in determining vitamin D status, the principal dietary source being fatty fish and the oils derived from them. Severe and marked vitamin D deficiency still occurs in many regions of the world, causing rickets in childhood and osteomalacia in adults. Recently it has been increasingly recognized that vitamin D insufficiency is common in the elderly, and particularly those who are no longer fully independent and therefore less exposed to sunlight. This problem is greater at higher latitudes. In addition, vitamin D insufficiency leads to secondary hyperparathyroidism and consequently to greater bone loss. It also impairs muscle metabolism and may increase the likelihood of falls.

When nutritional status with regard to vitamin D is assessed, the “normal” range — which varies with latitude — may not necessarily be optimal. It has been shown (31) that vitamin D supplementation suppressed levels of PTH only in subjects whose baseline serum 25-hydroxycholecalciferol was less than 50 nmol/l (20 µg/l). This suggests that 50 nmol/l is an appropriate threshold concentration for serum 25-hydroxycholecalciferol, below which individuals are at risk. However, some cross-sectional studies suggest that this threshold may be as high as 100 nmol/l (40 µg/l) (32).

Physiological supplements of calciferol (e.g. 400–800 IU/day) reduce PTH concentrations in elderly subjects and increase bone density, particularly at the femoral neck (33–36). Similar changes in biochemi-

cal end-points have been reported with regular exposure to sunlight for 15–30 minutes daily (35). The effect of calciferol supplementation alone on fracture rates has been assessed in two large studies. In the first (36), no difference in fracture incidence was found in 2578 Dutch men and women over the age of 70 years randomized to calciferol 400 IU/day or placebo. In the second (37), however, 150000 IU of vitamin D annually reduced symptomatic fracture rates by 25% in a cohort of 800 elderly subjects in Finland. In another study, in which calcium was co-administered with calciferol to elderly subjects (38), a reduction of more than one-quarter in all non-vertebral and hip fracture rates was reported in a cohort of 3000 elderly women given 800 IU of vitamin D and 1200 mg of calcium daily over a period of 3 years. A further randomized study comparing calcium (500 mg/d) plus vitamin D (700 IU/d) to placebo in 400 older men and women showed a reduction in non-vertebral fracture rates of more than one-half (39). Whether the calcium, the vitamin D or both together were responsible for reducing fracture rates is impossible to determine, though the most consistent results are in the two studies that used calcium plus vitamin D in the elderly (38, 39) (RRs of 0.45 and 0.75 in the respective studies, $P < 0.05$ for each). These studies show that it may be possible to markedly reduce morbidity in the elderly by means of a safe and inexpensive intervention.

Vitamin D supplements appear to produce no benefit in early postmenopausal women who are vitamin D replete (40). Their use as a physiological supplement is fundamentally different from the use of high doses of calciferol or 1α -hydroxylated derivatives of vitamin D to manipulate intestinal calcium absorption pharmacologically. These agents bypass the normal homeostatic control of vitamin D metabolism and therefore incur a significant risk of hypercalcaemia and hypercalciuria. The use of pharmacological doses of calciferol has not been demonstrated to confer any beneficial effects on bone density (41).

In conclusion, suboptimal vitamin D status is very common in the elderly, mainly because of reduced exposure to sunlight. A daily intake of 400–800 IU of vitamin D is a straightforward, safe and inexpensive means of prevention.

Other dietary factors

While much research has been focused on calcium intake, other dietary components may also be important. High intakes of protein, sodium and caffeine have all been reported to increase urinary

calcium loss in young adults, though reductions in bone density or elevations in fracture risk as a result have not been consistently demonstrated (see section 3.5).

Among the elderly, however, malnutrition does occur, e.g. as a result of a reduction in spontaneous food intake, malabsorption and intercurrent illness (42). The most common nutritional deficiency in the elderly is protein–energy malnutrition. Ageing is associated with a reduction in lean body mass which, combined with a decrease in physical activity, results in a significant decrease in energy requirements with advancing age (43, 44). In contrast to energy requirements, however, the need for other nutrients does not decline significantly with age. Whereas the recommended dietary allowance of protein in young adults is 0.8 g/kg of body weight, studies in the elderly have shown that, even when healthy, their requirement for protein is modestly increased, and a daily intake of 1 g/kg is recommended. Protein intake is therefore often inadequate in the elderly and protein restriction may be inappropriate.

In addition, randomized controlled trials have shown that protein supplementation in patients with recent hip fractures reduces subsequent bone loss and shortens hospital stays (45, 46). The clinical outcome is significantly improved by a daily oral protein supplement that normalizes protein intake, as shown by a reduction in complications such as bedsores, severe anaemia, and intercurrent lung or renal infections, and in the median duration of hospital stay (47). Other studies have confirmed normalization of protein intake, independently of energy, calcium or vitamin D, is responsible for this improved outcome (48).

It is possible that phytoestrogens, plant products with variable estrogen-like actions, may have a role in preventing postmenopausal osteoporosis. Laboratory and animal studies indicate that these compounds have beneficial effects on bone, but data from substantial clinical trials are not yet available. Low intakes of vitamin K may also increase the risk of hip fracture in women (49).

5.2.2 **Exercise**

The marked bone loss that follows skeletal disuse, e.g. in an immobilized limb or during prolonged bed-rest (see section 3.5.6), suggests that exercise may stimulate skeletal growth. In addition, a large number of cross-sectional studies in both sexes and at all stages of life have shown that bone density depends on customary activity levels (6).

However, such studies may be misleading since it is not clear whether physical attributes determine activity levels or the other way round, e.g. individuals with large muscles and therefore large bones, are more likely to take up weightlifting or other physically demanding pastimes.

While bone density is related to exercise levels, it is much less clear that customary exercise levels affect fracture risk. The European Vertebral Osteoporosis Study (EVOS) (50) suggested that high levels of physical activity were associated with increased risk of fracture in men, though the opposite was true in women. In contrast, the Tromso study (51) suggested that high levels of physical activity were protective against axial fractures in middle-aged men but not in women. The Study of Osteoporotic Fractures (SOF) (52) found that high levels of physical activity were associated with fewer hip fractures, but were unrelated to the risk of wrist or vertebral fractures. The interpretation of the results of these observational studies is complicated by the interaction of the effects of exercise on bone density, on the one hand, and on exposure to skeletal trauma on the other.

Because of the difficulties associated with observational studies mentioned above, randomized controlled studies have been used to determine the effects of exercise on bone. Such studies in prepubertal girls (53), premenopausal and postmenopausal women (54), and men (55) have found that exercise does have beneficial skeletal effects. Meta-analysis (56) of the effects of exercise on lumbar spine BMD showed a 1.6% (95% CI 1.0–2.2%) benefit on bone loss from impact exercise, and a 1.0% (95% CI 0.4%–1.6%) benefit from non-impact programmes in postmenopausal women. Results for premenopausal women were similar (1.5% [95% CI 0.6%–2.4%] benefit after impact exercise and 1.2% [95% CI 0.7%–1.7%] after non-impact exercise). Impact exercise programmes appeared to have a positive effect at the femoral neck in postmenopausal women (1.0%, 95% CI 0.4%–1.6%) and possibly in premenopausal women (0.9%, 95% CI 0.2%–2.0%). There were too few trials to draw conclusions from meta-analyses of the effect of non-impact exercise on BMD of the femoral neck.

These small benefits appear to be lost if individuals revert to an inactive lifestyle (57). Long-term compliance with intensive exercise regimens may also be poor. Drop-out rates approaching 50% have been recorded in some long-term clinical trials, and higher drop-out rates would be expected in the general population. In addition, some studies have found an increase in falls in subjects participating in exercise programmes (58). These factors suggest that such

programmes in older individuals will only have a small impact on fracture rates, and that the principal contribution of exercise may be to maintain muscle strength and thus prevent falls (see section 5.5).

The skeleton appears to be most susceptible to the benefits of exercise in childhood and adolescence. One randomized controlled trial in premenarcheal girls reported a 10% increase in femoral neck bone density among exercisers (53), and observational studies in which bone density in the playing arm of tennis and squash players was compared with that in the other arm, confirm that intense exercise during growth can result in residual skeletal benefits of this magnitude (59). Based on these findings, moderate physical activity should be encouraged throughout life but should be particularly emphasized during childhood and adolescence — the rapid expansion of electronic entertainment for children is a significant cause for concern in this regard. However, there is, as yet, no randomized controlled trial evidence that exercise prevents fractures. While exercise should be encouraged, it is not by itself an adequate therapy for those at high risk of fractures.

5.2.3 *Other measures*

Other lifestyle changes may also improve skeletal health, including cessation of smoking (section 3.5.7), avoidance of excessive alcohol consumption (section 3.5.8), and the maintenance of ideal body weight (see section 3.5.9). High body weight is associated with early puberty, particularly in girls. Delayed puberty in either sex is associated with persisting deficits in BMD throughout life.

5.3 **Pharmacological interventions in postmenopausal osteoporosis**

Several pharmacological agents have been approved or are being evaluated for the treatment of osteoporosis, and beneficial effects of these agents on bone turnover and/or BMD in postmenopausal women with or without prevalent fractures have been reported. However, adequate randomized controlled studies of their effects on fracture rates are not available for all agents. Available therapies include estrogens, estrogen derivatives and selective estrogen receptor modulators (SERMs), bisphosphonates, vitamin D and its analogues, and calcitonin. These act mainly by reducing bone resorption and bone turnover. The results of studies of the effects of antiresorptive agents on fracture incidence are summarized in the following sections. All patients undergoing pharmacological treatment for osteoporosis should be calcium and vitamin D replete. Finally, these studies were performed mainly in women with postmenopausal osteoporosis, and

Table 20
Evidence for the efficacy of therapies in osteoporosis

Intervention	BMD	Vertebral fracture	Non-vertebral fracture	Hip fracture
Calcium	A	B	B	D
Calcium + vitamin D	A	—	A	A
Estrogens	A	A	A	A
Tibolone	A	—	—	—
Alendronate	A	A	A	A
Etidronate	A	B	D	D
Risedronate	A	A	A	A
Ibandronate	A	—	—	—
Calcitonin	A	C	C	D
Fluoride	A	C	—	—
Anabolic steroids	A	—	—	D
Calcitriol	C	C	C	—
Alfacalcidol	C	C	—	D
Raloxifene	A	A	—	—
Ipriflavone	B	—	—	—
Menatetrenone	B	B	—	—

Evidence A, positive evidence from one or more, adequately powered, randomized controlled trials; B, positive evidence from smaller non-definitive randomized controlled trials; C, inconsistent results from randomized controlled trials; D, positive results from observational studies; —, efficacy not established or not tested.

their results cannot necessarily be extrapolated to men or to patients with other forms of osteoporosis. The evidence for the efficacy of the various therapies is summarized in Table 20. The different levels of evidence shown do not imply that one treatment is better than another, and comparisons between treatments have been made in only a few studies. Rather, the levels of evidence reflect the quality of the information on which efficacy is judged.

5.3.1 Estrogens

A wealth of evidence indicates that estrogens reduce bone turnover and prevent bone loss. Calcium supplementation amplifies this effect (60). Estrogen receptors have been demonstrated on osteoblasts and on other cells in the bone microenvironment but the precise mechanism of estrogen action is still unclear.

Many large observational studies have provided evidence of the anti-fracture efficacy of estrogens (61–67). However, fracture data from randomized, controlled trials in women with osteoporosis are scarce. A 10-year intervention study of 100 oophorectomized women found that estrogen reduced height loss and the number of vertebral

fractures (68). Another controlled study in 164 women found no fractures in the hormone replacement group and seven fractures in the placebo group during 10 years of treatment (69). In a 1-year study of the effect of transdermal estrogen and oral progesterone on the incidence of fractures in 75 women with one or more prior vertebral fractures (70), the incidence of new vertebral fractures was significantly reduced (8 in the estrogen group versus 20 in the placebo group) but not the number of patients with new fractures (7 versus 12, respectively). A randomized controlled trial in 464 early postmenopausal women reported a reduction in the incidence of non-vertebral fractures in those taking hormone replacement therapy (HRT) with vitamin D (71). Although no anti-fracture effect was found in a large study of HRT in women with pre-existing cardiovascular disease (72) a much larger clinical trial of 16000 women followed for 5 years showed a significant effect on a number of fracture end-points (hazard ratios for hip and vertebral fractures were both 0.66, and that for any fracture was 0.76, $P < 0.05$ for each) (73). These studies together with the observational data indicate that estrogens are an effective treatment for osteoporosis.

The optimal duration of estrogen treatment for skeletal health is not known, but observational data indicate that antifracture efficacy is reduced or lost 10 to 15 years after stopping treatment. This suggests that, as with other antiresorptive agents, long-term, continuous or intermittent treatment is required to achieve optimal effects. A variety of female hormone preparations are available, but all appear to have comparable effects on bone density if given in appropriate doses. Whether the addition of a progestin increases the effect of estrogen on bone is unclear (74, 75), although norethisterone, which has a mixture of progesteric, estrogenic, and androgenic effects, does have positive effects on BMD (76).

Estrogen affects many tissues other than the skeleton. Epidemiological evidence has suggested that it may reduce the risk of cardiovascular disease (77), but recent randomized controlled trials have not confirmed this and have suggested an increase in risk (72, 73). Uncertainty surrounds the effects of estrogen on cognitive function in women with and without Alzheimer disease (78). However, estrogen use for more than 5 years increases breast cancer risk (73, 79). Use of estrogen alone is known to increase endometrial cancer risk about 4-fold but the addition of continuous low-dose cyclic progesterone essentially eliminates this risk (73, 80). Estrogen use also increases the risk of venous thromboembolism 2- or 3-fold (71, 72). Many women will experience the return of menstrual bleeding, breast tenderness or headaches. These and other factors have contributed to generally

poor continuance with estrogens. They should not usually be taken by women with thrombophlebitis or thromboembolic disorders, breast, uterine or other estrogen-sensitive cancers, or postmenopausal bleeding of undetermined cause. Breast cancer in a first degree relative is sometimes considered to be a contraindication to estrogen use. Women taking estrogens should be monitored and undergo mammograms and regular breast examinations.

Although the cost of estrogen is low compared with that of other antiosteoporosis therapies of comparable efficacy, current uncertainties about extraskeletal effects make the formulation of policy difficult. All women considering the use of estrogen should be counselled regarding its risks and benefits. Long-term use of estrogen plus progestin appears questionable at this time, because of the recent evidence that it results in a net increase in adverse events (73).

5.3.2 ***Tibolone***

Tibolone is a synthetic steroid with combined estrogenic, progestogenic and androgenic properties related to variable receptor affinity of the parent compound and its metabolites. Its effects on bone density are comparable to those of estrogen or combined HRT (81). Its efficacy in reducing fracture risk has not yet been assessed. It is effective in controlling hot flushes and sweats and can also improve mood and libido. It does not cause endometrial proliferation in a dose of 2.5 mg daily, and withdrawal bleeds are therefore comparatively rare.

Women who receive tibolone should be at least one year postmenopausal to reduce the likelihood of uterine bleeding. Women who change from combined HRT to tibolone should be given cyclical progestagens until withdrawal bleeding ceases. The long-term effects of tibolone on cardiovascular morbidity have not been evaluated, but decreases in both very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) have been reported. The effects on high-density lipoprotein (HDL) are modest, if any.

5.3.3 ***Selective estrogen receptor modulators***

Raloxifene was the first selective estrogen receptor modulator (SERM) to be approved for the treatment and prevention of postmenopausal osteoporosis. It is a nonsteroidal benzothiophene compound with tissue-specific estrogen agonist and antagonist actions. It has beneficial effects on the skeleton and blood lipid levels, but does

not stimulate breast or uterine tissue. The recommended dose is 60mg/day.

In a study of 601 early postmenopausal women of mean age 55 years randomized to raloxifene or placebo, raloxifene prevented bone loss and induced a 1–2% gain in BMD in the spine, femoral neck, and total body (82). All the women in the study received 400 to 600mg of calcium daily, but raloxifene with calcium caused gains in BMD smaller than those usually seen with estrogens or potent bisphosphonates combined with calcium (60). It also lowered circulating levels of several bone turnover markers, including urinary type I collagen C-telopeptide and serum osteocalcin, but again these reductions were smaller than those seen with estrogens or bisphosphonates (82). In spite of the modest gains in BMD, a trial in 7703 osteoporotic postmenopausal women with or without prior vertebral fractures showed that raloxifene reduced the incidence of both clinical and radiographic vertebral fractures by about 30–50% after 3 years (RR of vertebral fracture 0.7, 95% CI 0.5–0.8, for the 60mg dose) (83). The study did not detect an effect on non-vertebral fractures (relative risk 0.9, 95% CI 0.8–1.1).

Among its non-skeletal effects, raloxifene lowers serum LDL cholesterol by 8–10% and total cholesterol by about 6% but, unlike estrogen, it does not raise HDL cholesterol levels (82). The effects on cardiovascular disease risk are not yet defined, though post hoc analyses suggest reduced vascular event rates associated with raloxifene use in those at high baseline risk (84). Use of raloxifene over 40 months was associated with a 76% reduction in new diagnoses of breast cancer when compared with placebo and, as seen with estrogens, an increase in incidence of venous thromboembolism (85). As expected, the drug does not cause breast tenderness or pain, nor does it induce endometrial thickening as determined by intrauterine ultrasound, or uterine bleeding. It does increase the incidence of hot flushes in a minority of women. The overall importance of raloxifene for postmenopausal women with osteoporosis will depend on the results of ongoing studies of its effects on cardiovascular disease and breast cancer risk.

Tamoxifen, a clomiphene analogue with weak estrogenic activity and one of the first SERMs to be developed for clinical use, is not licensed for use in osteoporosis, but has bone-sparing activity (86) and antifracture efficacy has been suggested (87). However, its use is associated with an increased risk of endometrial hyperplasia and occasionally carcinoma (88). It has been widely used in the adjuvant treatment of breast cancer and is undergoing evaluation in breast

cancer prevention. The use of tamoxifen (and possibly also raloxifene) may accelerate rather than prevent bone loss in premenopausal women.

5.3.4 **Bisphosphonates**

Bisphosphonates are synthetic analogues of pyrophosphate which suppress bone resorption and thereby reduce bone turnover. Nitrogen-containing bisphosphonates, such as alendronate, risedronate and pamidronate, may suppress bone resorption by a different mechanism from that of etidronate or clodronate, which do not contain nitrogen. A number of agents in this class have been evaluated in clinical studies, including etidronate, alendronate, risedronate, pamidronate, clodronate, tiludronate, ibandronate and zoledronate. Etidronate, alendronate and risedronate are most widely used in osteoporosis management at present.

Etidronate

Etidronate is given intermittently at 400 mg daily for 2 weeks followed by calcium 500 mg daily, in 13-week cycles. The efficacy of cyclical etidronate in preventing fractures in postmenopausal women with prevalent vertebral fractures has been investigated in several studies of similar design (89–91). Despite methodological problems in fracture assessment and limited statistical power, the combined results of these studies indicated that cyclical etidronate is probably effective in preventing new vertebral fractures in postmenopausal osteoporosis (RR 0.63, 95% CI 0.44–0.92) (22, 92). In contrast, meta-analysis does not indicate an effect on non-vertebral fractures (RR 0.99, 95% CI 0.69–1.42), though the total number of subjects studied is inadequate to address this question authoritatively (22, 92). There is no evidence from randomized controlled trials of the effect of cyclical etidronate on the risk of hip fracture, but post-marketing data suggest that it reduces the risk of non-vertebral fractures, including those of the hip (93). Cyclical etidronate therapy may also reduce the risk of fracture in glucocorticoid-treated postmenopausal women (94).

Alendronate

Alendronate has been studied extensively in randomized controlled trials. Most studies have assessed the effects of daily doses of 5 or 10 mg, though weekly doses of 70 mg have recently been shown to have effects on bone turnover and BMD comparable to those of the daily regimens, and are now widely used. In the initial 3-year study, alendronate was given in a range of doses to osteoporotic women (20% of whom had prevalent vertebral deformities), it significantly

reduced the incidence of new vertebral deformities (95). This effect was demonstrated when, as planned, the data for all the doses used were pooled. Its efficacy has since been investigated in two large populations of postmenopausal women, one with and one without pre-existing vertebral fractures (96, 97). All participants received supplementary calcium and vitamin D. In the vertebral fracture arm of this study (the Fracture Intervention Trial, FIT), 2027 women of mean age 71 years and with at least one vertebral fracture were treated with 5 mg daily for 2 years and 10 mg daily for the third year, or with placebo for 3 years (96). Treatment with alendronate reduced the incidence of clinical spine, hip and wrist fractures by about 50% ($P < 0.05$ for each). The treatment also decreased the incidence of new radiographically detected vertebral fractures from 15% over 3 years in the placebo group to 8% in the alendronate-treated group ($P < 0.05$).

The efficacy of alendronate in preventing fractures has also been investigated in 4432 postmenopausal women with no prior vertebral fractures (97). Women with hip BMD of 0.68 g/cm^2 or less (by Hologic scanner) were treated with placebo or alendronate 5 mg daily for 2 years and then 10 mg daily for the remainder of the 4-year trial. As in a previous study (95), alendronate increased BMD at all measured sites. Treatment with alendronate significantly reduced radiographic vertebral fractures (risk ratio 0.56, 95% CI 0.39–0.80) and there was a trend towards a reduction in all clinical fractures (risk ratio 0.86, 95% CI 0.73–1.01). A pre-planned subset analysis of the clinical fracture data, however, revealed that the treatment significantly reduced fracture rates among women with initial T scores below -2.5 (risk ratio 0.64, 95% CI 0.50–0.82) but not among women with T scores of -2.5 and above (risk ratio 1.08, 95% CI 0.87–1.35). The Fosamax International Trial (FOSIT) study has demonstrated a reduction in non-vertebral fracture incidence in postmenopausal women with a T-score below -2.0 (98), confirming that alendronate decreases clinical fracture rates in postmenopausal women with osteoporosis.

While alendronate prevents bone loss in normal postmenopausal women (99), its efficacy in preventing fractures in this group has not been demonstrated. It may also reduce the risk of fractures in glucocorticoid-treated postmenopausal women (100).

Risedronate

Risedronate has recently been shown to prevent fractures in osteoporotic women. In a randomized controlled trial of 2458 postmenopausal women with one or more vertebral fractures at trial

entry, treatment with risedronate 5 mg daily reduced the incidence of vertebral fractures by 41% (95% CI 18–58%) at the end of 3 years (101). In the same study, risedronate also significantly lowered the incidence of non-vertebral fractures by 39% (95% CI 6–61%). It has been shown to decrease the risk of hip fracture in a study of 9331 elderly women (RR 0.7; 95% CI 0.6–0.9) (102). In the subgroup of study participants with osteoporosis, the relative risk of hip fracture was 0.6 (95% CI 0.4–0.9), but in those selected primarily on the basis of non-skeletal risk factors, hip fracture risk was not significantly reduced. Meta-analysis of all risedronate studies shows a relative risk of vertebral fracture of 0.64 (95% CI 0.54–0.77), and of non-vertebral fracture of 0.73 (95% CI 0.6–0.87) (22).

Adverse effects of bisphosphonates

Bisphosphonates are poorly absorbed by the intestine and their absorption is further reduced by food, especially if it contains calcium. They should, therefore, be taken in the fasting state 30 to 60 minutes before a meal and only with water. At high doses, etidronate can cause osteomalacia. With the regimen used for osteoporosis, no clinically significant osteomalacia was reported in two large studies (103, 104), although there have been anecdotal reports of histologically confirmed osteomalacia in a small number of subjects (105, 106). Neither alendronate nor risedronate given to patients for up to 3 years impaired mineralization of newly formed bone (101, 107). Alendronate can cause irritation of the oesophageal and gastric mucosa, resulting in dyspepsia, heartburn, and nausea or vomiting. Although no differences in adverse effects between placebo and alendronate-treated patients were observed in clinical trials, a few cases of severe oesophagitis have been reported (108). Like alendronate, risedronate also has a safe profile in clinical trials. Post-marketing safety data are not yet available. Oral aminobisphosphonates should be used with caution in patients with oesophageal pathology (e.g. gastric reflux or achalasia) and instructions for their use should be carefully followed.

5.3.5 Calcitonin

Calcitonin is a peptide hormone with antiresorptive properties in bone. It can be administered either by subcutaneous injection or as a nasal spray. Nasal calcitonin reduces bone loss from the spine and hip in postmenopausal osteoporotic women (109, 110). A randomized prospective study of 134 women found a significant effect of intranasal calcitonin on the frequency of vertebral fracture when results for the three doses studied were combined (111). In a 5-year study of

1255 postmenopausal women of mean age 68 years with one or more prior vertebral fractures, nasal calcitonin 200IU daily significantly decreased the incidence of vertebral fractures by 36% (112). However, no reduction in fracture incidence was seen in women given either 100 or 400IU calcitonin daily. Both the calcitonin and control groups received 1000mg of calcium and 400IU of vitamin D daily. A recent meta-analysis of the efficacy of calcitonin concluded that there was significant heterogeneity in the published results, suggestive of publication bias, since the largest study showed the smallest effects (22, 113). They concluded, therefore, that the results of this large study (RR vertebral fracture 0.79, 95% CI 0.62–1.00; RR non-vertebral fracture 0.80, 95% CI 0.50–1.09) were the most reliable measure of the effect of calcitonin.

Nasal calcitonin has no serious toxicity and the only side-effect reported is rhinitis (23% for active treatment versus 7% for placebo) (109). Randomized controlled trials of both intranasal and parenteral calcitonin have shown that pain is decreased and remobilization hastened in patients with acute vertebral crush fracture syndrome (114).

5.3.6 ***Vitamin D metabolites***

The 1 α -hydroxylated metabolites of vitamin D are possible therapies for osteoporosis, but the results of controlled trials are inconsistent. Studies on Danish women in their fifties (115) and seventies (116, 117) showed no beneficial effects of calcitriol on bone loss, and suggested that it accelerated the rate of vertebral height loss. Similar negative findings in osteoporotic women have been reported (118, 119). However, increases in bone density in osteoporotic patients treated with calcitriol have also been reported (120, 121). A large but unblinded randomized controlled study found fewer fractures in patients receiving calcitriol in comparison with those treated with calcium alone (122). There are similar inconsistencies in the data available for alfacalcidol (123), though an observational study in Japan has suggested that hip fractures are less frequent in women taking this drug (124). A recent meta-analysis has found a reduced risk of vertebral fractures with vitamin D metabolites (RR 0.64, 95% CI 0.44–0.92) and a beneficial trend in non-vertebral fractures (RR 0.87, 95% CI 0.29–2.59) (125), though these findings are dominated by a single study (122).

Since a number of studies conducted in Japan have given positive results, it is possible that there are racial differences in responsiveness to these agents (126). Such differences might also be related to

differences in customary dietary calcium intakes, which are low in Japan, or differences in phenotype for the vitamin D receptor gene (127). Also, patients with low intakes of calcium may tolerate larger doses of vitamin D metabolites than those with higher intakes.

Several recent studies have suggested that vitamin D metabolites may have a role as an adjunctive therapy when given with an antiresorptive agent. Such a combination has a theoretical appeal since co-administration of these agents with an antiresorptive will minimize their capacity to stimulate bone resorption while leaving their beneficial effects on intestinal calcium absorption intact. Beneficial effects on BMD have been reported following the addition of calcitriol to alendronate (128), etidronate (129), and HRT (130), but no data on fracture rates are available.

5.3.7 **Fluoride**

Fluoride has been used for many years in the treatment of osteoporosis, although at much higher doses than those used in preventing dental caries. Several formulations of fluoride are available, including enteric-coated sodium fluoride, sustained-release preparations, and monofluorophosphates. The various formulations differ in their bioavailability and side-effects.

Fluoride has a direct anabolic effect on the osteoblast, possibly by potentiating the effects of endogenous growth factors (131). In osteoporotic patients, it induces substantial increases in BMD at sites of cancellous bone, particularly in the spine. Annual rates of increase of spinal BMD as high as 8% have been reported over 4 years (132). However, high fluoride concentrations can interfere with normal bone mineralization; this may explain why fluoride-induced increases in bone density do not consistently reduce fracture rates (132, 133). In those studies that have suggested that fluoride use reduces fracture rate (134–136), these positive results may be related to the use of slow-release preparations (134) or to low fluoride doses (136) although, in the Fluoride and Vertebral Osteoporosis Study (FAVOS), neither the dose nor the type of formulation influenced outcome (133). Recent meta-analyses (22) suggest a decrease in vertebral fractures (RR 0.67, 95% CI 0.38–1.19) but confirm that there is significant heterogeneity in the data. For non-vertebral fractures, the trend found in the meta-analysis is in the opposite direction (RR 1.46, 95% CI 0.92–2.32).

Because of the inconsistency of the data, fluoride has not been recommended for widespread use in the management of osteoporosis, and is best reserved for use by specialists. In some countries, very high

concentrations of fluoride are found in water supplies and give rise to endemic fluorosis, so that the therapeutic use of fluoride salts should be undertaken with even greater caution in individuals from these areas.

5.3.8 **Other agents**

Thiazides

The use of thiazide diuretics is associated with reduced urinary calcium excretion, and some observational studies have found that thiazide users have higher BMD and reduced risk of hip fracture (137). However, these findings might be accounted for by higher body weight and higher bone mass in hypertensive patients, the principal group using thiazides. Two randomized controlled trials of thiazides in normal older women have recently documented increases in BMD of about 1% over treatment periods of 2 to 3 years (138, 139). These small effects on BMD may be large enough to influence fracture risk with long-term use. Thus, like calcium, thiazides may have a role as a preventive intervention, but are unlikely to be adequate as monotherapy for established osteoporosis.

Anabolic steroids

Anabolic steroids are testosterone analogues modified to reduce their virilizing effects. However, these modifications are only partially successful, and the long-term clinical use of 17 β -esterified derivatives such as nandrolone is limited by the development of acne, hirsutism and voice changes. Nevertheless, anabolic steroids do produce increases in bone density comparable to those associated with HRT (140). The 17 α -alkylated agents, such as stanozolol, have significantly less virilizing effects, but prolonged use may increase hepatic transaminases. No prospective randomized studies to determine whether anabolic steroids reduce fracture frequency have been carried out. A case-control study has shown that the use of anabolic steroids in women was associated with a significant decrease in the risk of hip fracture (141). The extent to which anabolic steroids function as promoters of bone growth *in vivo* is uncertain, and some studies suggest that their major effect is to decrease the rate of endocortical bone resorption.

Ipriflavone

Ipriflavone is a synthetic flavinoid which appears to have some estrogenic activity, and is available in some countries for the treatment of osteoporosis. Randomized clinical trials have produced inconsistent

effects on bone density (142, 143) and there are no data from randomized controlled studies on its ability to reduce fracture rates.

Vitamin K

Low serum concentrations of vitamins K₁ and K₂ have been reported in patients with osteoporosis, and serum osteocalcin appears to be undercarboxylated in these individuals, a process dependent on vitamin K. Undercarboxylated osteocalcin is also a significant risk for hip fracture. Clinical studies in Japan suggest that menatetrenone (vitamin K₂) reduces skeletal losses and, in a small randomized clinical trial, it reduced the rate of vertebral fractures (144). Menatetrenone is currently used in Japan, the Republic of Korea and Thailand.

Parathyroid hormone

Parathyroid hormone (PTH) and its analogues have shown marked effects on BMD and fracture rates, both when used alone (145) and in combination with an antiresorptive agent (146). The largest study to date (145), randomized 1637 postmenopausal women with prior vertebral fractures to receive 20 or 40 µg of parathyroid hormone [1–34] or placebo daily for a median duration of 21 months. New vertebral fractures occurred in 14% of the women in the placebo group and in 5% and 4%, respectively, of the women in the 20 µg and 40 µg parathyroid hormone groups. The respective relative risks of fracture in the 20 µg and 40 µg groups, as compared with the placebo group, were 0.35 and 0.31 (95% CIs 0.22–0.55 and 0.19–0.50). New non-vertebral fractures occurred in 6% of the women in the placebo group and in 3% of those in each parathyroid hormone group (RR, 0.47 and 0.46, respectively; 95% CIs 0.25–0.88 and 0.25–0.86). PTH is well tolerated in human studies, though occurrences of bone tumours have been reported in long-term, high-dose safety studies in rats. PTH is not yet available for clinical use.

5.3.9 Future therapies

Many combinations of different agents have shown additive effects on BMD, but there is currently no evidence that such combinations have greater effects on fracture risk than single agents. Much research is currently being done to develop new pharmaceuticals for the treatment of osteoporosis, particularly those with anabolic effects on osteoblasts. Strontium, statins and osteoprotegerin, among others, are currently being investigated.

5.4 Pharmacological intervention in other contexts

5.4.1 *Men*

Despite the growing acknowledgement that osteoporosis is also a problem in men, few trials of strategies for its management have been conducted. There is anecdotal evidence supporting the use of testosterone replacement in hypogonadal men, and of etidronate. Randomized controlled trials have shown beneficial effects of fluoride (147) and alendronate (148) in men, but a much larger experience in men is required before recommendations can be made.

5.4.2 *Glucocorticosteroid-induced osteoporosis*

Osteoporosis resulting from the long-term use of glucocorticoid drugs is one of the secondary osteoporoses for which interventions have been assessed (149). Discontinuation of corticosteroid results in a modest increase of BMD, but alternate-day steroid regimens appear to have effects on bone density comparable to those of daily administration. The local administration of glucocorticoids substantially reduces their systemic effects, though some systemic availability occurs with virtually all routes of administration. The efficacy of calcium and calciferol is uncertain, since recent studies of this combination have produced contradictory results (150, 151). The bisphosphonates have produced positive effects on bone density in a number of studies, and there is evidence of fracture prevention with alendronate (100), risedronate (152), and possibly etidronate (94). Sex hormone replacement increases bone density in both steroid-treated men (153) and women (154). There is also some evidence supporting the use of calcitonin (155), fluoride (156), calcitriol (157) and alfacalcidol (158).

5.5 Minimization of skeletal trauma

Skeletal trauma may be reduced either by preventing falls or by minimizing their consequences. Normal vitamin D status probably makes an important contribution to optimal muscle function and thus to fall prevention. Exercise may reduce fracture risk by increasing postural stability and decreasing the frequency of falls (159). A meta-analysis of seven trials of exercise intervention in the elderly found a 10% reduction in the fall frequency (160). Comprehensive programmes aimed at preventing falls that also involve interventions such as assessment by a physician with adjustment of medications, assessment by an occupational therapist with appropriate referral, behavioural instruction, and attention to environmental safety (e.g. improving lighting, removing rugs and cords likely to cause falls, providing hand rails) can reduce the frequency of falls by 30–60%

(161–163). Because of the importance of falls in the etiology of hip fracture in particular, programmes such as these in the frail elderly could reduce the frequency of fractures. No study to date, however, has found a significant reduction in fracture rates. Prevention of falls is nevertheless important since the fear of further injury may result in decreased activity, further muscle loss, and thus an increased risk of further falls.

The minimization of skeletal trauma following falls is a new area of research. There is evidence that the use of hip protectors can reduce fracture rates by more than 50% (164, 165), though achieving compliance with these devices has been difficult. The use of shock-absorbing surfaces in the home, particularly on floors, may also reduce the likelihood of fracture following a fall (166).

5.6 Other measures

This section has dealt mainly with pharmaceutical interventions for fracture prevention, but the management of osteoporosis must be more broadly based. Other measures include the prevention and treatment of falls and the use of physiotherapy and physical exercises in patients with established osteoporosis. In addition, physical therapy is of particular value, following fractures.

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6. **Socioeconomic aspects**

6.1 **Introduction**

The need for socioeconomic factors to be taken into account is increasing in all types of health care since the resources available are limited but demand continues to increase. With the exception of the USA, most countries allocate less than 10% of their gross domestic product (GDP) to health care, and this is usually all that they are prepared to spend. A careful choice of priorities is therefore necessary, and osteoporosis is unlikely to be given a high priority since a consensus definition of this condition was accepted only 10 years ago (1), and only in 1994 were operational definitions established (2, 3). Osteoporosis, therefore, unlike other chronic diseases, is not widely accepted as a major burden to society, nor is it generally agreed that it can effectively be identified and treated.

The first step in any socioeconomic evaluation is to determine the burden of the disease in question. For osteoporosis, this is usually the burden of fractures, which can be expressed in terms either of the number of fractures or of the resulting costs. However, the risk of osteoporotic fractures varies widely, and the various types of osteoporotic fracture differ markedly in clinical significance at different ages and in costs in different regions. Nevertheless, such evaluations are useful in highlighting the impact of osteoporosis and the savings that prevention or treatment can bring.

6.2 **Methods of socioeconomic evaluation**

The burden of osteoporosis can be expressed either in numerical or financial terms. This is an important step in documenting its impact and in comparing it with other major diseases. Economic considerations are also important in patient management and in therapeutics, where pharmacoeconomic models are used to assess treatment and prevention strategies, to justify intervention thresholds and to plan future strategies, including drug development. However, societies, patients, physicians, pharmaceutical companies, regulatory agencies and health care purchasers all have quite different perspectives, so that what may be of advantage to one segment of the community may not be to another. In addition, if osteoporosis is treated, something else may have to be neglected. For this reason, it is useful to express the outcome of various interventions in common terms so as to make comparisons possible.

6.2.1 *Types of evaluation*

The most straightforward type of pharmacoeconomic evaluation is cost-minimization analysis, which can be used when two strategies or pharmaceutical agents have identical effects, e.g. both decrease fracture rates by a certain percentage and neither has adverse effects. The advantage of one over the other will then only be in the cost, either of the treatment or of the whole strategy. The price of a drug administered orally, for example, may be the same as that of one given intravenously, but the total cost may differ markedly.

In practice, the benefits and risks of different strategies are rarely the same and this difference is taken into account in determinations of cost-effectiveness. Outcomes are therefore expressed in terms of, e.g. the cost per life-year saved, the decrease in time to remission or the cost per fracture saved. However, comparisons between diseases are difficult, and difficulties also arise even with the same disease. The cost per fracture averted, for example, is not the same for a hip fracture and a forearm fracture.

A widely used measure in osteoporosis is the “number needed to treat” (NNT) to prevent a fracture. For example, if a treatment reduces the incidence of vertebral fractures from 10% to 5% during a trial, five fractures are saved for each 100 patients treated, which gives a NNT of 20. However, the NNT takes no account of the cost of intervention, and its use is relevant only to the trial population. In the example quoted, the efficacy of the intervention is 50%, but for the same efficacy in other populations at different risk, the NNT changes. Thus, if the background risk is, say, 5% and treatment reduces this by half, $NNT = 40$. A further problem with the use of NNT is that it takes no account of the offset of the effect of therapeutic intervention (4).

Expressing benefits in terms of costs rather than events is therefore preferred. Cost–benefit analysis expresses both benefits and costs in monetary units, but this type of analysis cannot take account of differences in the morbidity associated with different events or strategies. This is important in chronic diseases such as osteoporosis, where the consequences of fracture, and particularly hip fracture, may be vastly greater than the financial cost.

These considerations have led to the development of cost–utility analysis, which takes account not only of fractures avoided, but also of any change in their attendant morbidity. Quality-adjusted life-years (QALYs) are accepted units of measurement in the evaluation of interventions based on cost–utility. To estimate QALYs, each year of life is valued according to its utility, which may vary from 0, the least

desirable health state to 1, or perfect health. The decrease in utility associated with fractures is the cumulative loss of utility over time. WHO favours disability-adjusted life-years (DALYs), which have been extensively used to characterize the burden of disease worldwide (5), but not yet of osteoporosis.

6.2.2 *Nature of costs*

Direct costs include direct hospital costs, which differ from direct health-care costs, and those, in turn, differ from direct non-medical costs, such as the costs of transporting patients to and from hospitals and the cost, e.g. of buying calcium supplements. Indirect costs are usually those associated with the patient's loss of income, e.g. as a result of taking time off work following a fracture, but, in addition, for some fractures, the impact on careers and the household in general is not negligible. Intangible costs are, by definition, those that are difficult to quantify in monetary units and, in osteoporosis, are mainly those of the morbidity associated with osteoporotic fractures.

Economic evaluations of osteoporosis are summarized below.

6.3 **Burden of illness**

The burden of osteoporosis in terms of the number of fractures has been evaluated in several national studies, but little information is available on the numbers of osteoporotic fractures worldwide. An exception is hip fracture, and future trends are reviewed in sections 1.3 and 3.1. No cohesive attempt has been made to translate this into a global economic burden, because the costs of health care differ as widely as do the patterns of treatment. For example in the United Kingdom, the average duration of hospital stay after a hip fracture is close to 30 days (6), whereas in Sweden it is closer to 15 days. In a large southern European study, the Mediterranean Osteoporosis study (MEDOS), a substantial minority of hip fractures were treated conservatively in Portugal, whereas in many other countries the overwhelming majority were treated surgically (7). Even characterizing the burden of disease in a single country is problematic in the sense that there are many different types of fracture, each with different consequences. The vast majority of hip, forearm, vertebral and proximal humeral fractures after the age of 50 years are osteoporotic in nature. The incidence of several other fractures increases with age, and these have been associated with low BMD (8), but there is no consensus on what constitutes an osteoporotic fracture. In women, candidates include rib and tibial fractures and, if these are neglected the burden of disease will be underestimated, to the disadvantage, in particular, of the younger age groups, in whom the ratio of

these fractures to hip fracture, for example, is much higher than in later life.

6.3.1 **Economic cost**

All estimates indicate very substantial costs. In England and Wales, for example, the cost was recently estimated at £942 million each year (9), and this figure will probably increase as the numbers of elderly people increase. In the USA, direct medical expenditures on osteoporotic fractures (see Table 21) were estimated at US\$ 13.8 billion in 1995 (10).

Financial analyses of the costs of osteoporosis have been mainly, though not exclusively, of the classic osteoporotic fractures (11). Such analyses clearly indicate that hip fracture has the highest costs of all osteoporotic fractures. For example, in the USA, the average direct cost of hip fracture was estimated at US\$ 21 000 in the first year, that of a vertebral fracture was US\$ 1200 and that of a Colles fracture US\$ 800 (11). In other countries, the costs are lower but hip fractures are still the most costly. Thus the cost of a hip fracture in the Hong Kong SAR was estimated at US\$ 10 820 in the first year and that of a Colles fracture at US\$ 600 (12). Age also affects costs, and direct costs for hip fracture are twice as high in the elderly than in younger patients. The type of treatment and length of hospital stay of the patient are very important determinants of fracture costs. Thus, the proportion of the total expenditure accounted for by hip fractures compared with other fractures is greater the longer the survival of individuals (and therefore the average age) within a particular geographical region. Hip fracture costs are the highest because of the long duration of hospital stay. In the USA, hip fractures account for 63% of the total health care expenditure on osteoporosis (13). In the Netherlands, they account for about 85% of the hospital costs of osteoporosis (Figure 12), of which 80% is due to hospitalization (Figure 13) (14, 15). In the United Kingdom, hip fracture accounts for more than 90% of hospital bed-days due to osteoporosis (6). Indeed, hospitalization for hip fracture accounts for direct medical costs comparable with those for many other chronic diseases in the Netherlands (14), Sweden (16) (Figure 14) and the United Kingdom (6).

Several national studies have quantified the current costs of all osteoporotic fractures. In the USA, for example, the annual direct medical costs of osteoporosis were estimated to be US\$ 5200 million (17) in women aged 45 years and older in 1986. Inpatient care accounted for US\$ 2800 million, nursing home care for US\$ 2100 million and outpatient care for US\$ 200 million. It has been estimated

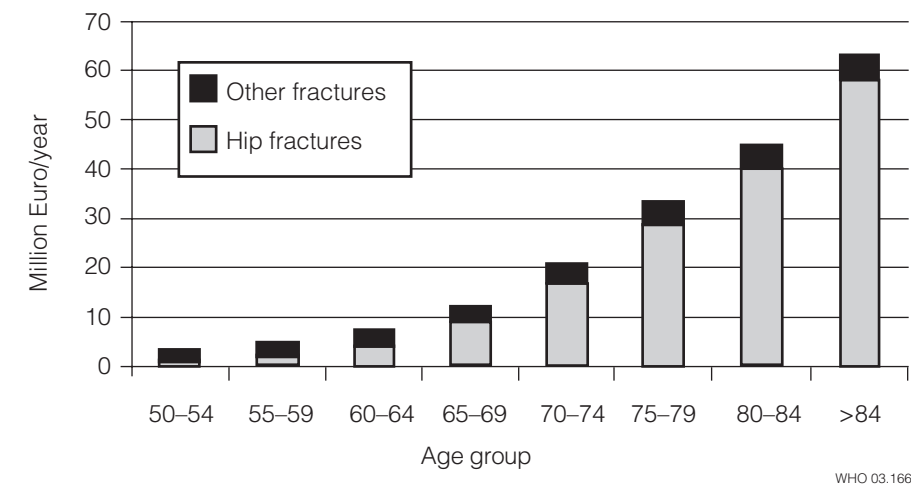
Table 21

Health care expenditures attributable to osteoporotic fractures in the United States by type of service and fracture

Type of fracture	Type of service (millions of US\$)					
	Inpatient hospital	Emergency room	Outpatient physician	Outpatient hospital	Other outpatient ^a	Nursing home
Hip	5576	130	67	9	90	2811
Forearm	183	55	93	8	4	41
Spine	575	20	13	3	10	126
All other sites	2259	362	297	45	91	899
Total	8594	567	470	65	194	3875
						8682
						385
						746
						3953
						13764

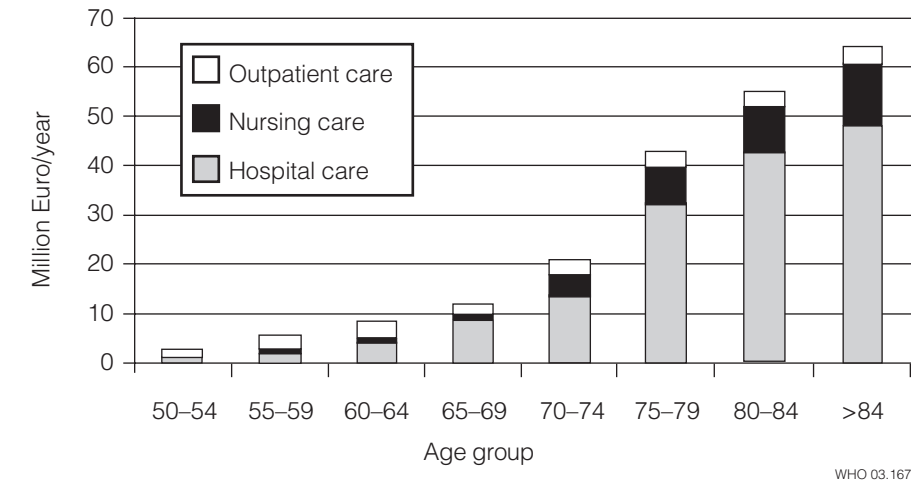
^a Includes home health care, ambulance services and medical equipment.
Modified from *Journal of Bone and Mineral Research*, 1997, **12**:24–35 (10) with the permission of the American Society for Bone and Mineral Research.

Figure 12
Total direct medical costs per year of hip and other osteoporotic fractures by age in the Netherlands^a



Hip fractures accounted for 85% of total direct medical costs.
^a Reproduced from reference 14 with the permission of the authors.

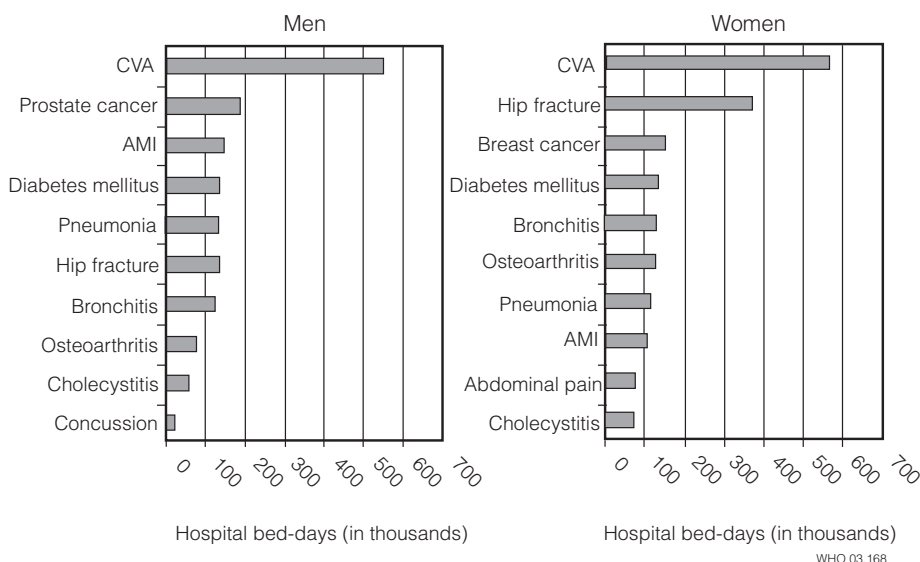
Figure 13
Contribution of different types of care to the total annual cost of osteoporotic fractures in the Netherlands, 1993^a



^a Reproduced from reference 14 with the permission of the authors.

Figure 14

Burden of disease as measured by hospital bed-days in Sweden^a



CVA, cerebrovascular accident; AMI, acute myocardial infarction.

^a Based on data from reference 16.

(18) that, in the next decade, there would be 5.2 million hip, spine and forearm fractures among women over the age of 45 years in the USA, and therefore 2 million person-years of fracture-related functional impairment, and US\$ 45 200 million of total health care expenditures.

From prospective data from Australia, it has been estimated that the average cost of fractures treated in hospitals was US\$ 7000 and that of fractures treated in outpatient clinics was US\$ 300 (13). Femoral neck fractures were the most expensive to treat, at US\$ 10 700 each. Of the direct costs of all osteoporotic fractures, 95% were incurred by hospitalized patients. In a worldwide projection of the annual cost of hip fractures, current costs were estimated at US\$ 3600 million in men and US\$ 19 300 million in women. By 2050, these costs would rise to US\$ 14 000 million for men and US\$ 73 000 million for women. Such estimates are, of course, highly conjectural.

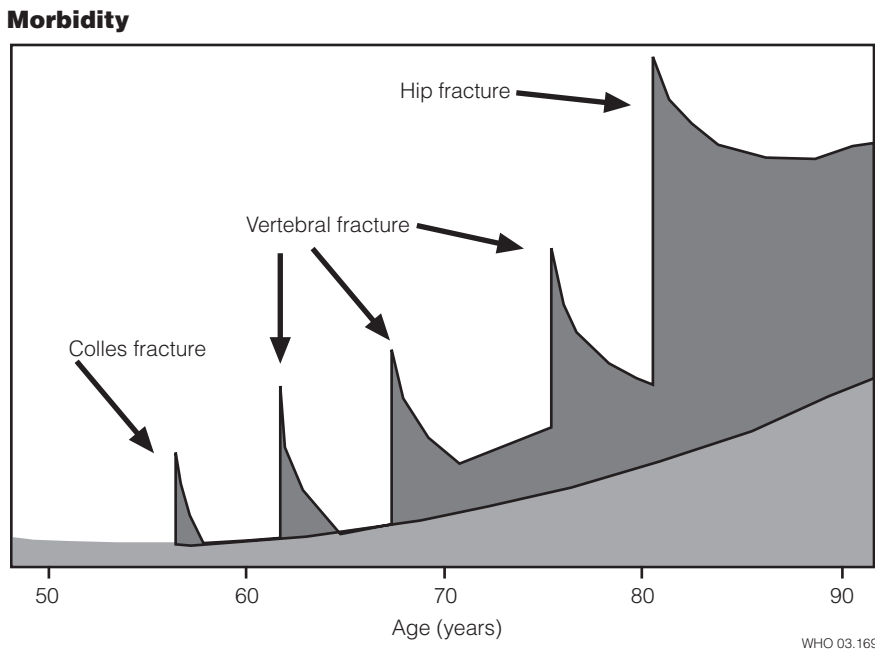
In the USA, medical expenditure has been assessed by sex and ethnicity (19). Of US\$ 13 800 million spent on the treatment of osteoporotic fractures in 1995 for persons aged 45 years and over 75% was spent on treating white women, 18% for treating white men, 5% for treating non-white women and 2% for treating non-white men

(19). Of the total cost, 62.4% was for inpatient care, 28.2% for nursing home care and 9.4% for outpatient care, consistent with estimates from other Western countries. These relative costs cannot be universally applied because the risk of fracture and the sex ratio vary widely, e.g. in some developing countries, osteoporotic fractures are as prevalent in men as in women (20–22).

6.3.2 **Morbidity**

Different types of fracture cause different degrees of morbidity (23), as shown schematically in Figure 15. Colles fractures almost invariably have only short-term sequelae, whereas the morbidity from vertebral fractures increases with the number of fractures and, with multiple fractures, can result in permanent impairment. The most serious fracture is hip fracture, which typically causes long-lasting morbidity. Since hip fracture accounts for the highest morbidity, and hip fracture rates increase with age, morbidity is also expected to

Figure 15
Morbidity associated with different osteoporotic fractures with age^a



Cumulative morbidity from osteoporosis (darker shaded area) adds to baseline morbidity changes (lighter shaded area) with age. Colles fracture commonly occurs in women in their mid-50s and has short-term sequelae. Repeated vertebral fractures occurring at a later age may give rise to permanent morbidity. Hip fractures usually occur on average at the age of 80 years in developed countries and usually give rise to permanent morbidity.

^a Reproduced from reference 23 with the permission of the publisher.

Table 22
Utility loss associated with different osteoporotic fractures

Fracture site	First year	Subsequent years
Vertebra	0.0502	0.0490
Ribs	0.0502	0.0490
Pelvis	0.0502	0.0490
Humerus	0.0464	0.006
Clavicle, scapula, sternum	0.0464	0.006
Hip	0.4681	0.1695
Other femoral fractures	0.4681	0.1695
Tibia and fibula	0.4681	0.1695
Distal forearm	0.0464	0.006

Based on data from reference 24.

increase with age. However, other osteoporotic fractures contribute to morbidity and are therefore important in younger individuals.

The National Osteoporosis Foundation has estimated the morbidity arising from different types of osteoporotic fracture (24). As expected, morbidity in terms of utility losses is greater for hip fracture than for most other fractures (Table 22), but the method of deriving the weights used by the expert panel differ from those used in other studies (25–27). Patients with osteoporosis tend to put less emphasis on their disability than that accorded by the general population (25). Nevertheless, rank order of disability from different fracture types is likely to be similar.

6.4 Population-based prevention strategy

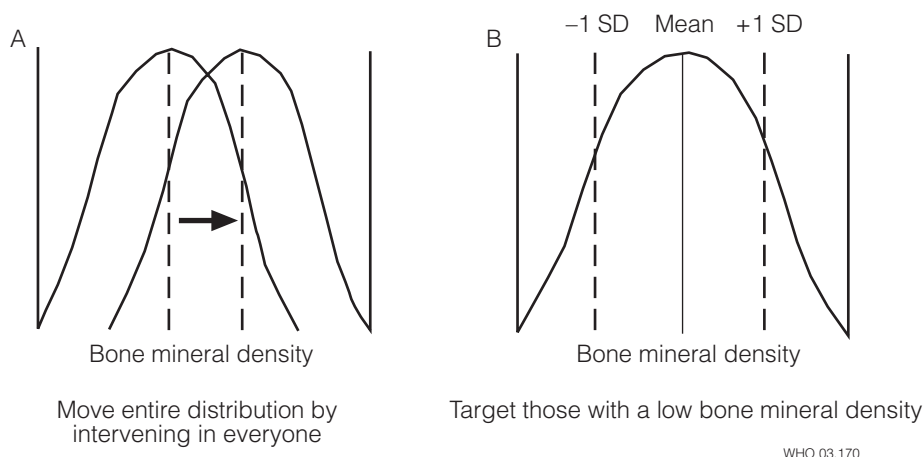
Most of the world’s ageing population lives in developing countries where neither bone densitometry nor drugs for osteoporosis are available. The population-based prevention strategy is therefore the only practicable choice in these countries.

In contrast to screening (see section 6.5), the population-based prevention strategy aims to raise the average BMD by nationwide intervention (Figure 16). A rise in BMD by 10% in the whole population might be expected to decrease fracture rates by 20% (28), although this estimate may be conservative.

Eliminating the risk factors that have been identified might significantly reduce the burden of osteoporosis. Obvious interventions include raising levels of exercise, stopping smoking, and increasing dietary intake of calcium (28–30). There are, however, several problems with these approaches. Thus not all of these factors are necessarily causally related to osteoporosis. In addition, although several

Figure 16

Distinction between a population-based strategy and screening strategy to alter bone mineral density



The population-based strategy (left panel) aims to shift the population distribution to the right, whereas the screening strategy (right panel) targets individuals with low BMD.

clinical trials have shown the beneficial effects of exercise on bone mass or loss, this would probably need to be sustained for a lifetime. Bone loss is likely to occur soon after exercise is stopped, and long-term continuance is likely to be very low. The value of exercise for 5 years to a patient at the age of 40 years is therefore questionable when the individual reaches the age of 75 years. In the case of exercise, the optimum type and duration are also not known.

Of the prevention strategies available, the strongest case can be made for increasing calcium intake. Both epidemiological and randomized controlled trials show that high intakes of calcium reduce rates of bone loss and prevent fractures (see section 5.2.1). The impact on hip fracture risk of a population approach aimed at increasing calcium intake has recently been assessed (31), based on the MEDOS study in southern Europe, where high intakes of calcium were associated with a decreased risk of hip fracture. From estimates of attributable risk, causality and reversibility, such a strategy might prevent only up to 1.67% of hip fractures in an elderly community because only about 10% of the population has a low intake of calcium. The impact would be much greater in populations where low intakes of calcium (or vitamin D) are more prevalent, e.g. in nursing homes. The selection of high-risk groups increases the attributable risk (Table 23) and thus the potential impact of eliminating the risk factor.

Table 23
Estimates of attributable risk derived from the prevalence of risk factors and their relative risk

Population with risk (%)	Relative risk			
	1.5	2	2.5	3
5	2.4	4.7	7	9.1
10	4.8	9.1	13	16.7
20	9.1	16.7	23.1	28.6
30	13	23.1	31	37.5
50	20	33.3	42.9	50

This does not mean that lifestyle advice and encouraging exercise are not worth while, since the benefits of some interventions are not limited to skeletal health. An example is provided by exercise since exercise programmes for subjects over the age of 65 years have been found to be cost effective with a cost per quality of life-years saved ranging from £100 to £15 000 (32). Studies aimed at evaluating the impact and feasibility of population programmes in osteoporosis prevention are strongly recommended.

6.5 Screening

Screening is used to select healthy individuals for intervention, and differs from opportunistic case-finding, which is sometimes also called screening. The advantage of screening is that it is an extension of the physician/patient relationship in the sense that the intervention is considered appropriate by the individuals concerned and motivation on the part of both patients and physicians is high. Disadvantages include the costs of screening as well as the limited contribution to disease prevention in the community as a whole. Major criteria for the evaluation of screening programmes are summarized in Table 24 (2).

To justify a screening programme a disease must have been demonstrated to be an important health problem and its natural history must be adequately understood. Both these criteria may be assumed to be met by osteoporosis in Caucasian populations (see sections 1.3 and 3.1). The natural history of osteoporosis, in the context of screening, is also well delineated. The pattern of change in BMD with age is reasonably clearly understood, and the independent contribution of BMD to fracture risk has been unequivocally demonstrated.

Table 24
Major criteria for the evaluation of screening programmes

Aspect	Criteria
Disease	— An important social problem
	— Natural history adequately understood
The test	— Simple and safe
	— Acceptable to the population
	— Effective: sensitive and specific
The intervention	— Accepted and effective treatment available
	— Agreed policy on whom to treat
The programme	— Facilities for diagnosis and treatment
	— Cost-effective

Adapted from reference 2 with permission from the publisher.

6.5.1 **Screening at the menopause**

Because bone loss in women occurs at menopause, a readily diagnosable event, it has been argued that screening of women by means of bone densitometry at the menopause should be considered. There are, however, several problems with respect to the test that might be used for screening. The most obvious candidate is testing of BMD. Many relatively short-term prospective studies indicate a 1.5–2.5-fold increase in fracture risk with each standard deviation reduction in BMD (see section 4.4).

There have been several analyses of the potential utility of screening at the menopause (2, 33–39) all of which found that the cost of screening is not the dominant factor since most treatments are relatively expensive. Opinions vary on the use of BMD (33), but widespread screening at the menopause on the basis of BMD alone is not generally recommended because of the poor sensitivity and specificity of BMD measurement when used for screening. Screening is aimed at directing interventions to those in need and to avoiding the treatment of healthy individuals who have a low risk of fracture. Tests should therefore be of high specificity, perhaps of the order of 90% or more. To achieve this degree of specificity, approximately 10% of the post-menopausal population might be selected as a high-risk category (40) (Table 25). On this assumption, the sensitivity of the test is low. If it is assumed risk increases 1.5-fold for each standard deviation decrease in BMD, the sensitivity or detection rate is only 18%. If a gradient of risk of 2.5 per standard deviation decrease (i.e. the prediction of hip fracture from hip BMD) is taken, sensitivity is still only 34% (40). In this scenario, 1000 patients would need to be screened to detect 100 for treatment, and the maximal impact on the

Table 25
Estimates of positive predictive value, sensitivity and specificity of measurements to predict hip fracture over 15 years or to death in women aged 50 years according to different population cut-offs to define a high risk category

Gradient of risk (RR/SD)	High risk category (% of population)														
	0.5			5			10			15			25		
	PPV	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec
1.5	3.9	1.5	99.5	2.8	11.0	95.1	2.3	18.3	90.1	2.2	26.5	85.1	1.9	38.0	75.2
2.0	7.5	3.0	99.5	4.4	17.1	95.2	3.4	26.6	90.2	3.1	36.4	85.3	2.5	48.8	75.3
2.5	11.8	4.7	99.6	5.9	23.1	95.2	4.3	34.0	90.3	3.8	44.5	85.4	2.9	57.1	75.4
3.0	16.4	6.5	99.6	7.2	28.5	95.3	5.1	40.3	90.4	4.3	51.1	85.5	3.2	63.4	75.5

PPV, positive predictive value (%); Sens, sensitivity (%); Spec, specificity (%).

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community after menopause (percentage of hip fractures saved) would be approximately 7% (40). This assumes 50% efficacy of intervention and 100% compliance over 15 years, somewhat over-optimistic assumptions indeed.

There are also problems with treatment following screening at the menopause. While randomized controlled studies show that treatments are effective (see section 5.3), continuance with treatment is poor. Thus with HRT, only about 10% of women in the USA continue treatment for more than 1 year (28), but uptake and continuance are likely to be improved by screening (41), so that the return on investment is correspondingly low. Even where treatments are taken for extended periods, their ultimate effect depends not only on the effect induced, but also on the offset of effect when treatment is stopped. Where effects persist after stopping treatment, the fractures saved and benefit are greater than where the effects wear off rapidly (42). A recent analysis of cost-effectiveness quantified the importance of “offset time” (4). In health economic terms, costs of US\$ 30 000 per QALY gained represent reasonable cost-effectiveness in developed countries. If it is assumed that the effect of a treatment wears off after about 5 years, targeting treatment at women with a relative risk of 2.0 at age 50 years would cost US\$ 370 000 per QALY gained for an expensive treatment, and US\$ 269 000 for a cheaper one (4). Estrogens and biphosphonates probably have a relatively slow offset time, but this is much shorter than the 5 years for other therapeutic modalities. On the reasonable assumption that women at age 50 years are unlikely to take lifelong treatments, it would be difficult to persuade health care agencies that such an approach is worth while. Moreover, the costs of screening have not been included.

6.5.2 *Screening in later life*

Screening may, however, be justified if higher-risk individuals can be selected. In one approach, individuals much older than 50 years are selected because the risk of fractures increases exponentially with age (43, 44). Indeed, there is an age above which the risk of fracture is sufficiently high to justify intervention without screening. A possible example is the use of vitamin D in the elderly, where it has been estimated that if such a regimen prevented 10% of hip fractures, there would be savings to the health care system (44). Another approach is to select individuals at higher risk than is suggested on the basis of age or BMD alone. Combining BMD with other risk factors, such as clinical risk factors, biochemical markers or bone turnover, has been reviewed in section 4.5. There may, therefore, be a case for screening in later life with the use of factors that add to the value of

BMD. Such approaches substantially increase the sensitivity of assessments without any loss of specificity (40).

6.6 Case-finding

Because of the problems associated with population screening at the menopause, and because screening at later ages has not yet been validated, attention has turned towards case-finding (opportunistic screening), as outlined in section 4.5. In this scenario, patients with clinical risk factors are identified for further assessment, most commonly by the measurement of BMD. Guidelines on the indications for BMD measurement have been published by the International Osteoporosis Foundation (formerly the European Foundation), the US National Osteoporosis Foundation, the Osteoporosis Society of Canada and the Royal College of Physicians in the United Kingdom (24, 29, 45–47).

Economic analyses of the European guidelines indicate that treatment can be cost-effective. Typical costs are US\$ 2100 per fracture averted for a treatment that costs US\$ 300 per year, and compare favourably with those for the management of other chronic disorders. Moreover, using BMD assessment in conjunction with risk factors increases cost-effectiveness. For a treatment that costs US\$ 75 per year and reduces fracture by 50%, skeletal assessment is of uncertain benefit. While BMD assessment saves resources compared with assessment of risk factors alone, the amount saved is small. However, cost-effectiveness increases as the cost of treatment increases. A treatment costing US\$ 300 per patient per year and reducing fracture risk by 50% over a 5-year period gives a cost per fracture averted of US\$ 550 using densitometry as compared to US\$ 1800 without BMD assessment. Thus, the cost-effectiveness of the case-finding strategy increases as the costs of the treatment rise (45).

The National Osteoporosis Foundation has published a detailed economic assessment set within a target of intervening at costs below US\$ 30000 per quality of life-year saved (24). Unlike the European guidelines (45), they recognize that individuals with a combination of risk factors might benefit from treatment at a BMD less than the criterion for osteoporosis adopted by a WHO Study Group (see section 4.3.1). The National Osteoporosis Foundation has published a practical guide for physicians (46), in which assessment by BMD measurement is recommended for all women aged 65 years and over. For postmenopausal women under 65 years, BMD measurement is recommended in the presence of one or more risk factors, including Caucasian race and female sex. The National Osteoporosis Founda-

tion guidelines recommend that physicians should offer treatment if the T-score is less than -2.0 in the absence of risk factors and less than -1.5 when they are present. The differences between the recommendations in different countries (48) indicate the need for strategies that can be applied worldwide but also that take into account local factors, e.g. the very different risks that exist in different countries.

6.7 Cost-effectiveness of pharmaceutical intervention

The vast majority of economic evaluations have been devoted to HRT (49–58). The use of HRT for menopausal symptoms has been found to be cost-effective, with a cost of £700–£6200 per QALY gained (52). Most authors have also found favourable cost-effectiveness ratios with long-term use (53–58), while the cost per life-year gained fell as the duration of treatment increased (58). In addition, a combination of estrogen and progestogen was more cost-effective than estrogen alone (54). However, all these analyses are extremely sensitive to assumptions that may be erroneous about the effects of HRT on cardiovascular disease.

Fewer data are available for treatments that affect skeletal metabolism alone (50). There is also a paucity of information on indirect costs, so that true costs may be considerably underestimated. The use of a model (59) showed treatments with an efficacy of approximately 50% were cost-effective and that their cost-effectiveness compared favourably to that of the treatment of mild hypertension. However, in this analysis, it was assumed that the effects of treatment over a 5-year period would persist for the remainder of life after treatment was stopped, whereas the available evidence suggests that this is not correct (43). The most extensive analysis is that carried out by the National Osteoporosis Foundation (24), but some details of the types of costs used are not given. Other economic analyses have either made unreasonable assumptions (e.g. treatment for life) (60), or used denominators that do not apply to other health care environments (61).

Nevertheless, several broad conclusions can be drawn. First, treating more elderly individuals is more cost-effective since the absolute risk of fracture is higher. Similarly, the selection of individuals at high risk due to age is more cost-effective. Second, a high cost of intervention adversely affects cost-effectiveness, and third, the offset time has a marked impact (4). Some of these factors are illustrated for hip fracture in women in Table 26 (4). With a threshold of US\$ 30000 per QALY gained, it is cost-effective to prevent hip fracture in women aged 70 years or over who have a 2-fold increase of hip fracture where

Table 26

Effects of a 5-year intervention to prevent hip fracture in women by age, relative risk of hip fracture and intervention costs^a

Age (years)	Relative risk	Cost (US\$)	Savings (US\$)	Life-years gained	QALYs gained	Cost/life-year gained (US\$, thousands)	Cost/QALY gained (US\$, thousands)
<i>Intervention cost \$625 per year</i>							
50	1.0	2900	180	0.0005	0.004	5690	745
60	1.0	2840	400	0.0040	0.010	604	240
70	1.0	2740	805	0.0212	0.027	91	70
80	1.0	2500	1480	0.0625	0.059	16	17
50	2.0	2890	345	0.0007	0.007	3904	370
60	2.0	2840	760	0.0067	0.019	310	110
70	2.0	2725	1460	0.0369	0.049	34	26
80	2.0	2450	2550	0.1072	0.103	savings	savings
<i>Intervention cost \$250 per year</i>							
50	1.0	1160	180	0.0005	0.004	2055	269
60	2.0	1160	345	0.0007	0.007	1245	118
70	1.0	1140	405	0.0040	0.010	182	72
80	2.0	1140	760	0.0067	0.019	55	20

^a The effect of treatment is assumed to have an offset time of 5 years.

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the cost of intervention is US\$ 625 per year. With a cheaper treatment (US\$ 250 per year), it is cost-effective to treat 60-year-old women at high risk. Although much further work needs to be done, it is clear that the treatment of high-risk patients can be cost-effective, but more precise definitions of high risk are needed and the assumptions made must be reasonable.

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7. **Delivery of care and education**

Concerted action is needed at both international and national levels to develop a coordinated strategy to deal with osteoporosis and reduce its burden on society. Increasingly, national and international nongovernmental agencies have brought together health professionals, government officials and the public to promote health care, health policy, and health education on osteoporosis and public awareness of the disease. A number of international guidelines have been developed (1–3), and their principles should be incorporated into local protocols and formularies.

This section is concerned with the organization of osteoporosis care at the national level and the education of the different segments of the population.

7.1 **Delivery of care**

Proper provision for osteoporosis needs a clear structure, adequate facilities and arrangements for the reimbursement of health care costs, effective guidelines, and mechanisms for monitoring the system.

7.1.1 **Structure of provision**

In the past, osteoporosis has largely been managed by specialists, but its prevalence and the increasing number of patients identified suggest that its management will be the responsibility of primary care physicians, who will, however, need expert advice and specialist diagnostic facilities.

The ability of primary care physicians to manage osteoporosis effectively is severely restricted in a health system without specialized services for osteoporosis. A combination of primary care and specialist multidisciplinary facilities, and strategies that are developed nationally and interpreted locally, will ensure an integrated approach to the care of patients with osteoporosis (4).

The primary care sector is becoming increasingly responsible for the clinical care of chronic conditions such as osteoporosis as a consequence of changes in clinical practice. Primary health care teams are likely, therefore, to be responsible for, or advise on, activities that include health promotion for the general population, identification and follow-up of high-risk individuals, early identification and management of patients, and their referral, when appropriate, for diagnostic investigation and specialist advice.

The objective of a specialist-based (often hospital-based) facility is to provide a comprehensive clinical service in support of primary care. This clinical service should be reserved for patients with complicated or difficult problems on which consultant advice will be required. In addition, referrals to central facilities will be required for assessment by bone densitometry and other diagnostic investigations, such as biochemical tests or X-rays, for the early detection of osteoporosis and for monitoring progress. These assessments may be offered independently of a full-scale clinical service. Specialists, in association with primary care teams, should also develop local guidelines to ensure consistent management of osteoporosis and provide standards for audit and quality assurance. Expert clinicians can provide specialist input in health promotion programmes, and can also update generalists in the management of osteoporosis. An effective osteoporosis service requires a multidisciplinary team of health professionals, headed by a clinician with expertise in osteoporosis.

A local strategy for osteoporosis care and the proper organization of health professionals within the district should be developed by local osteoporosis planning and coordinating teams that include representatives of primary and secondary care, and local health care commissioners. These commissioners should incorporate the local osteoporosis strategies into their purchasing plans and allocate resources for the clinical service. A district strategy for osteoporosis should depend on evidence-based recommendations developed at the national level, but also on other priorities and resources. Such recommendations should be formulated by an appropriately skilled and experienced national osteoporosis planning and coordinating group, which should be responsible for launching a comprehensive national osteoporosis programme. Countries differ markedly in socio-economic development, culture and environment so that the priorities and problems of such groups will vary considerably. Some of the issues that need to be considered are shown in Table 27, while potential members of such groups are listed in Table 28. National groups should work closely with national scientific and patient societies, the ministry of health, associations of health professionals, insurance companies and medical schools. WHO's global strategy for osteoporosis may also be implemented by such national groups.

The proposed structure of osteoporosis care is shown in Figure 17 and has been found to be effective in Hungary (5).

7.1.2 *Facilities for diagnosis and treatment*

Facilities for the diagnosis and treatment of osteoporosis are inadequate in many countries. Radiological examinations and routine

Table 27

Checklist of issues that need to be considered by national osteoporosis planning and coordinating groups

-
- What is the size of the problem of osteoporosis in the country?
 - How should osteoporosis care be structured?
 - What arrangements will be made for shared care among different health care providers (primary and secondary care physicians, nurses, etc.)?
 - How will medical care be linked to community health facilities and educational initiatives?
 - What are the major preventable causes of osteoporosis in the country?
 - Which population groups are at special risk?
 - What treatments are currently used?
 - What other treatments are available and affordable?
 - Who will be responsible for the education of health professionals?
 - Who will be responsible for the education of patients?
 - How can osteoporosis education and prevention be integrated into other programmes?
 - How can graduate medical education on bone diseases be improved?
 - How can facilities and reimbursement of costs for the diagnosis and treatment of osteoporosis be improved?
 - How can the effectiveness and quality of care be monitored?
-

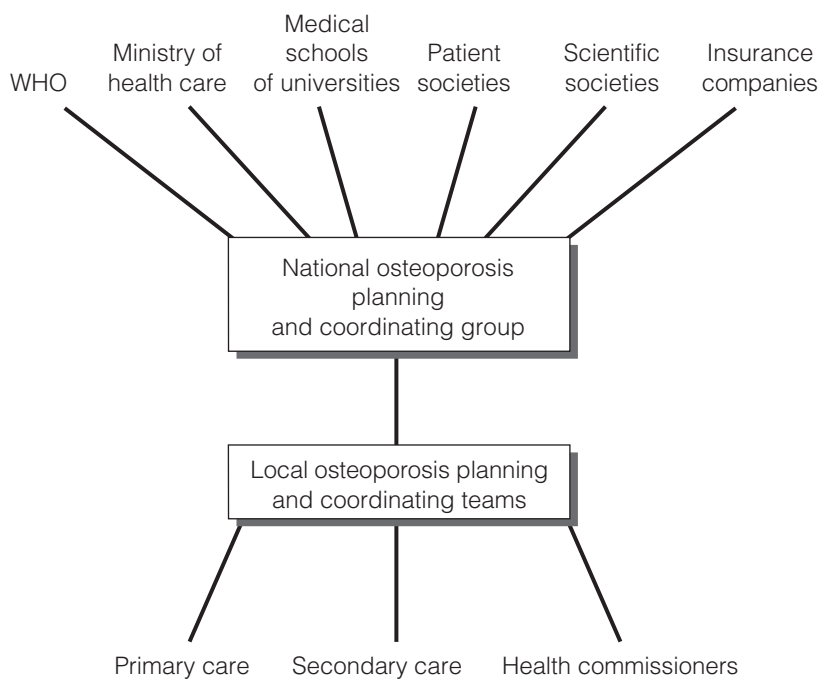
Table 28

Possible members of a national osteoporosis planning and coordinating group

-
- Lead specialist
 - Other specialists in rheumatology, endocrinology, gynaecology, orthopaedic surgery, paediatrics and geriatrics
 - Primary care physicians
 - Nurses/exercise therapists
 - Health commissioners and policy-makers
 - Health educational specialists
 - Health economists
 - Medical sociologists
 - Representatives of patient support groups
 - Journalists, mass media specialists
-

biochemical tests for calcium metabolism (serum and urinary calcium, serum and urinary phosphate, serum alkaline phosphatase) are available in most primary and secondary care establishments. However, access to investigations for the exclusion of other metabolic diseases and secondary causes of osteoporosis (serum, PTH, $1\alpha,25$ -dihydroxycholecalciferol, TSH (thyroid-stimulating hormone), testosterone, gonadotropins, free cortisol) is rather limited worldwide. Although specific serum and urinary markers of bone turnover may

Figure 17
Proposed structure of osteoporosis care



WHO 03.171

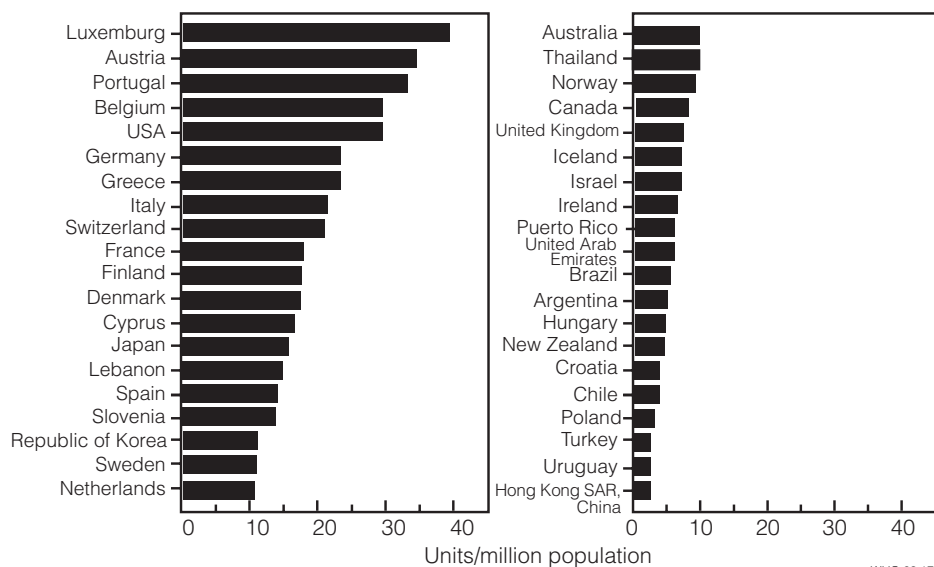
be helpful in monitoring treatment, their availability is even more limited.

Measurement of BMD can be used to assess fracture risk, confirm the diagnosis of osteoporosis, and monitor the effects of treatment. Early detection of bone loss is the key to preventing unwanted complications. Although BMD measurements provide the best method for the diagnosis of osteoporosis, population-based screening cannot be justified and only patients at high risk should be selected for densitometry (see sections 4.5, 6.4 and 6.5) (1, 2).

The availability of bone densitometry systems throughout the world varies greatly (Figure 18). Many doctors and their patients do not currently have access to bone density measurements, particularly in many Asian countries. There are also marked variations in available resources even between countries of the European Union (3), where the average number of bone densitometers and ultrasound units ranged from 6 to 40 per million of the population. Similar variations are found in other geographical regions (3, 6) (see Figure 18). Access to bone densitometry can be increased by the use of

Figure 18

Estimated numbers of bone densitometry systems (per million population)



WHO 03.172

The estimate includes axial, appendicular and ultrasound equipment. (Data compiled by the International Osteoporosis Foundation: from JA Kanis, unpublished data, 2000, and proprietary information kindly provided by Hologic, IGEA srl, Lunar Corporation and Norland Medical Systems.)

mobile equipment, but quality control of such systems must also be ensured.

The number of hospital beds dedicated to patients with hip and vertebral fractures is inadequate in most regions of the world. The incidence of osteoporotic fractures will rise steeply in the future, so the need for orthopaedic beds will also increase. Since the incidence of hip and vertebral fractures is approximately the same and about 10% of patients with vertebral fractures need hospital care in the acute phase, hospital admissions for both fracture types can be estimated to be 110% of the incidence of hip fracture (7). The total number of hospital beds available in the countries of the European Union currently exceeds 2.8 million. If there is no significant increase in this number the proportion used for patients with hip and vertebral fracture will rise from 0.88% to 1.97% (3). This may be offset by measures designed to reduce the duration of hospital stay, but only a few countries have the effective and unified rehabilitation programmes necessary for the early discharge of patients with osteoporotic fractures.

Apart from the shortage of densitometry equipment and hospital beds, there are too few specialists with adequate expertise in bone diseases. The unique biology of bone and the increasing burden of osteoporosis suggest that the management of bone disease should be a distinct medical specialty or, in some countries, a recognized component of accreditation in another specialty. A consultant with specialist knowledge of osteoporosis and metabolic bone diseases is required to lead the secondary care service and the local osteoporosis planning and coordinating teams. This expert may be drawn from one of the many clinical specialties involved in osteoporosis management, and should head a team including related specialists, densitometry assistants, physiotherapists and nurses. Those performing bone densitometry and interpreting the results must have undergone the necessary training and obtained a certificate to that effect (8, 9).

7.1.3 *Reimbursement of health care costs*

The costs of conventional radiological and laboratory investigations are usually adequately reimbursed, as are those for hospital care for patients with osteoporotic fractures. Reimbursement of bone densitometry measurements, however, is lacking, partial or restricted in many countries, and this limits their use even where resources are available. In many countries which offer reimbursement, methods of reimbursement will have to be changed if interventions are based on risk of fracture, rather than a given diagnostic threshold. Biochemical markers are used in several countries, but their use is reimbursed only in a few countries.

Effective drugs are available for the prevention and treatment of osteoporosis and others are being developed. Unfortunately, many patients do not have access to these drugs in several African, Asian, and South American countries and also in some European countries. Mechanisms for the reimbursement of bone-active agents differ markedly, and the extent of reimbursement varies from 0% to 100% in different countries. The proportion of osteoporotic individuals who receive treatment is usually not higher than 5–10%, even in developed countries.

7.1.4 *Guidelines*

Guidelines on the diagnosis and management of osteoporosis help to set standards of clinical care and may serve as a basis for audit. They can also provide a starting point in the education of health professionals, and may therefore be used to ensure that all members of primary or secondary care teams are aware of the goals and methods of management of osteoporosis.

Several comprehensive international guidelines on the assessment and management of osteoporosis have been developed, including those formulated by the European Foundation for Osteoporosis (now the International Osteoporosis Foundation) and the report on osteoporosis by the European Community (1, 3, 10). However, international guidelines may improve quality of care and reduce morbidity only if they are adapted at national and local levels so as to increase the sense of ownership and relevance. Guidelines should therefore always be adapted and distributed by local osteoporosis teams that are aware of the regional characteristics of the population and of osteoporosis care. They are often most useful when they include summary charts of the key recommendations for diagnosis and management, because such charts can easily be copied so that health professionals can use them when advising patients.

7.1.5 *Monitoring care process and outcome*

In addition to systems to deliver care to patients with osteoporosis, a system for monitoring the effectiveness and quality of care is also essential. Monitoring involves the surveillance of conventional epidemiological parameters, such as the prevalence and incidence of osteoporosis and fractures, as well as the audit of both care process and outcome. To do this effectively, minimum sets of data to be audited should be defined. Each country should determine its own minimum targets for audit.

The auditing process should cover the implementation of guidelines in clinical practice relating to diagnostics, differential diagnosis and treatment, and the presence or absence of counselling on diet, exercises and lifestyle. Auditing outcome may relate to the effect of pharmacological and non-pharmacological interventions on BMD, the occurrence of different fractures, pain and the quality of life of patients.

7.2 Education

Ignorance about osteoporosis is still common among health professionals, patients and the public; education is therefore needed by all these groups. The aim of a programme of education and communication is to increase knowledge of bone physiology and osteoporosis, to raise awareness of major risk factors, and to provide information on the possibilities of primary and secondary prevention, and the management of osteoporosis. Good education should reduce morbidity and mortality, keep people at work, and decrease direct health costs. There is an increasing need for nongovernmental organizations to interact with health professionals, government agencies and the

public to adopt common approaches to public awareness, education and policy. Web-based education may also be useful.

7.2.1 *Education of health professionals*

The education of health professionals should be coordinated in each country by the national group (see section 7.1.1) and local osteoporosis planning and coordinating teams and may be targeted to specialists, primary care physicians, nurses, densitometry assistants, physiotherapists, exercise therapists, occupational therapists, dietitians, social workers, pharmacists, employees of pharmaceutical companies, diagnostic and insurance companies and officials of the ministry of health. The methods used in continuing education differ widely and include lectures, training courses, scientific journals, video cassettes and the Internet. Teaching should include mechanisms to perpetuate the messages and thereby increase its effectiveness.

Information on bone and mineral physiology and bone diseases should be provided, not only in postgraduate courses, but also as part of undergraduate education. Bone and mineral metabolism should be recognized either as part of a wider specialty or as an independent specialty. When no specialty is responsible, no one will take the lead in education or the delivery of care. Postgraduate courses at both the international and local level are also needed to inform specialists on progress in bone diseases.

7.2.2 *Patient education*

In patient education programmes, the emphasis should be on the development of an ongoing partnership between health professionals, the patient and the patient's family, so that patients can contribute to their own well-being. The aims of patient education are:

- to increase understanding among patients;
- to increase skills;
- to increase satisfaction among patients;
- to increase confidence; and
- to increase continuance of treatment and self-management.

Because better education of health professionals ensures that patients receive the most appropriate treatment, a concerted effort is required to ensure adequate continuance. Continuance of medication by patients with osteoporosis can be increased if:

- the patient believes that his or her disease is, or will be, a problem;
- the patient believes that he or she is at risk;

Table 29
Factors involved in noncompliance

Drug factors	Non-drug factors
• Cost of medication • Distance from pharmacies • Dislike of medication • Awkward regime • Side-effects • Difficulties with administration (nasal spray, injections, etc.)	• Misunderstanding or lack of instruction • Dissatisfaction with health professionals • Poor supervision, training or follow up • Underestimation of severity • Anger about condition or its treatment • Fears about side-effects • Inappropriate expectations • Cultural practices or religious beliefs • Forgetfulness

- the patient believes that the treatment is safe;
- the patient feels in control; and
- there is good communication between the patient and the health professional.

Noncompliance may be defined as the failure of the patient to take the treatment as directed by the health professional. Factors involved in noncompliance are listed in Table 29.

Patient education should provide the patient with suitable information and training. Patients can acquire information about the disease and its treatment by:

- listening to health professionals;
- reading books or leaflets, watching videos, or listening to audio tapes;
- attending courses on osteoporosis;
- attending public meetings or patient support groups to learn from other patients with osteoporosis;
- reading articles in magazines or newspapers;
- watching television programmes or listening to the radio;
- accessing Web-based information that may be available world-wide;
- other activities such as World Osteoporosis Day (20 October) organized by the International Osteoporosis Foundation.

The basic information to be given to patients with osteoporosis is outlined in Table 30.

Patient education is aimed at changing behaviour, and not just providing information. Change will occur only if patients are given an adequate opportunity as part of the educational process to express their

Table 30

Basic information for patients with osteoporosis

-
- Understanding of the disease and its consequences
 - Methods of diagnosis
 - Results of the BMD measurements
 - Types of treatment available
 - Expectations of both the disease and its treatment
 - Diet, exercise, lifestyle, other risk factors
 - Methods of preventing falls and fractures
 - Individual activity plan for the future
 - Regular supervision and reinforcement
-

fears and concerns. They must be able to discuss with health professionals their expectations in the context of the condition and its treatment, and be told how realistic those expectations are. Social and psychological support may also be required to maintain positive behavioural change, and there is an important role here for patient support groups.

Core information must be personalized and given to the patient in a number of stages. At the initial consultation, the patient with osteoporosis needs information about the nature of the disorder, the types of treatment available, and the rationale for the specific therapeutic interventions being recommended. Verbal information should be supplemented by written (or pictorial, for patients with poor literacy) information about osteoporosis. In early consultations, an individualized activity plan should be drawn up specifying what the patient must avoid or undertake. At follow-up consultations, the patient's questions should be answered, and any problems with osteoporosis and its initial pharmacological and non-pharmacological treatment discussed. The patient's understanding of the information and management skills should be assessed periodically.

The purpose of self-help or support groups is to help patients to help themselves to manage their illness. Many patients benefit from joining such groups as an adjunct to education by health care professionals. Their activities vary from country to country and area to area, but most provide information, opportunities for group education, discussion and mutual support. Teaching osteoporosis patients and their families how to cope psychologically and to take charge of their lives is as important as medication. Self-help groups can help patients to avoid hospitalization and institutional care and thereby reduce the considerable burden of osteoporosis. A recent study in Germany demonstrated that anxiety was reduced and bone density

significantly increased in the members of an osteoporosis self-help group compared to non-members receiving identical therapy (11). Such patient support groups exist in a number of countries, and some are listed in the Annex.

7.2.3 *Education of the general public and other groups*

The education of the general public about osteoporosis is helpful since it enables members of the public to recognize the symptoms of the disease and to identify individuals at risk. The press, radio and television can play a valuable part here, provided that information is disseminated responsibly. Politicians and health administrators also need an adequate knowledge of the disease. Schoolteachers, and especially those teaching physical education and biology, can help young adults to maximize their peak bone mass.

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8. Summary

8.1 Epidemiology of osteoporosis

The prevalence of osteoporosis increases markedly with age in women. According to the criteria suggested by a WHO Study Group, namely a BMD 2.5 standard deviations or more below the average for the young healthy female population, by age 75 years, approximately 30% of Caucasian women would be classified as having osteoporosis, based on BMD at the femoral neck of the hip. The clinical consequences of osteoporosis are the result of fractures, the incidence of which increases as BMD decreases.

Hip, forearm and vertebral fractures are most closely associated with osteoporosis although fracture risks in other bones are increased among those with osteoporosis. Hip fractures account for most of the morbidity, mortality and costs of the disease. For example, among those living independently before a hip fracture, only about half are able to do so after it. Hip fracture rates increase exponentially with age. At 80 years, a Caucasian woman has about a 3% annual risk of hip fracture.

Important clinical risk factors for hip fracture include low body weight, tallness, a personal history of fracture, a family history of fracture, smoking, use of glucocorticoid steroids and physical inactivity. Genetic factors are important, although specific genes remain to be identified. Few studies of risk factors have been conducted on hip fractures in ethnic groups other than Caucasians or in men.

Vertebral fractures are also strongly related to age, but even more strongly to menopause. They are also more common in women than in men, and more common among Caucasians than among African-Americans. Rates among Asians are variable but are generally midway between those in Caucasians and African-Americans. The consequences of vertebral fractures include back pain and disability, kyphosis and height loss. The risk of osteoporotic fractures in the future is greatly increased among those with vertebral fractures. Little is known about other clinical risk factors for vertebral fractures.

In some countries the incidence of forearm fracture increases 10-fold in women in the 15 years following menopause, but remains fairly constant thereafter.

Independently of age, the risk of fracture for postmenopausal women is about three times that for men: the lifetime fracture risk for a Caucasian woman is about 15%. Compared with Caucasians, blacks have about one-third, and Asians and Hispanics about half the risk of hip fracture.

An estimated 1.7 million hip fractures occurred throughout the world in 1990. Since both world population and life expectancy are increasing, that number is expected to rise to 6.3 million by 2050. Currently, the majority of hip fractures occur in Europe and North America. However, demographic shifts over the next 50 years will lead to huge increases in the numbers of the elderly in Africa, Asia and South America. Consequently, the burden of the disease will shift from the developed to the developing countries. By 2050, 75% of the estimated 6.3 million hip fractures will occur in the developing countries. Prevention strategies suitable for these countries will therefore need to be developed and implemented.

8.2 Pathogenesis of osteoporosis and related fractures

Bone serves several important functions in the body: protection against trauma, locomotion and provision of a calcium phosphate reservoir. It is a specialized form of connective tissue composed of an organic matrix mineralized by the deposition of calcium phosphate. This gives rigidity and strength to the skeleton together with some elasticity. Morphologically, there are two forms of bone: cortical or compact, and cancellous or spongy.

Bone is a living tissue, and is constantly resorbed and formed by the process known as remodelling, so that bone formation takes place not only during growth but also throughout life. Osteoblasts are the cells responsible for bone formation while osteoclasts are specialized cells that resorb bone. During growth, bone formation exceeds bone resorption. From the age of 30 to about 50 years, the amount of bone formed approximately equals the amount resorbed. From the time of the menopause in women and perhaps later in men, bone resorption exceeds bone formation. The mass of bony tissue present at any time during adult life is the difference between the amount accumulated, i.e. the so-called peak bone mass, and that lost with ageing.

Pathogenetic factors favouring the osteoporotic process are those impairing bone mass accumulation during growth and those accelerating bone loss during later life. Individuals vary markedly in peak bone mass, which is mainly determined by body size. Heredity is also a determinant of peak bone mass, as are the degree of physical activity and calcium intake.

The acquisition of bone mass during growth may be impaired by factors such as bed rest due to illness, and undernutrition or malnutrition, particularly when associated with low calcium and protein intakes. Several paediatric disorders impair optimal gain of bone mass. In some diseases, such as glucocorticoid excess or growth hormone

deficiency, the abnormal bone mass accrual can be attributed to a change in a single hormone. In other disorders, such as anorexia nervosa and exercise-associated amenorrhoea, the cause is a combination of malnutrition and deficiency of sex steroid hormones. Severe chronic paediatric diseases requiring immunosuppressive treatment that may include glucocorticosteroids and chemotherapies or radiotherapies can adversely affect bone formation.

During late adulthood, hypogonadism is a major cause of bone loss and is the main cause of postmenopausal osteoporosis. At the menopause, estrogen deficiency causes an increase in bone turnover resulting in an imbalance between bone formation and resorption. The pathophysiological mechanism involves the release in the bone marrow of cytokines, such as tumour necrosis factors and interleukins, that stimulate osteoclastic bone resorption. In men, loss of bone may be associated with low rates of bone formation rather than high rates of bone resorption, which in turn may be due to declining levels of gonadal hormones. Other endocrine diseases such as primary hyperparathyroidism, hyperthyroidism and hypercortisolism can induce bone loss. In the elderly, low calcium intake associated with a reduced endogenous production of vitamin D (vitamin D insufficiency) accelerates bone loss, probably by increasing the secretion of PTH.

8.3 **Diagnosis and assessment**

Osteoporosis was not classified as a disease until relatively recently, since it was considered to be a condition that expressed itself as fractures. Now, an internationally accepted definition describes osteoporosis as a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. This provides the framework for an operational definition on the basis of BMD measurements. As previously mentioned, a WHO Study Group defined osteoporosis in women as a BMD 2.5 standard deviations or more below the average for the young healthy female population. The same absolute BMD value can provisionally be used for men, although data on BMD and fracture risk in men are sparse.

There is considerable lack of uniformity in the presentation of BMD values, in part due to technical differences in equipment, differences in normal ranges, and the complexity of the computer output. Uniform criteria should be used for diagnosis using the T-score for BMD measured at the hip.

The hip is the preferred site for diagnostic assessment, particularly in the elderly, using dual-energy X-ray absorptiometry, although other

sites and techniques are useful in assessing risk and in some cases, response to treatment. The emphasis on hip measurement arises from the clinical importance of hip fracture and the strength of the relationship between BMD at this site and the risk of hip fracture. Prospective studies have shown, however, that the risk of fracture in general increases progressively the lower the BMD, regardless of measurement site. For each standard deviation decrease in BMD, fracture risk increases by approximately 50%. The ability of BMD to predict hip fractures is better or at least as good as that of the measurement of blood pressure to predict stroke.

Although bone loss occurs in women at the menopause, universal screening by BMD is not justifiable at this time. The use of other risk factors in addition to BMD improves performance characteristics, as does the assessment of older people. Until such strategies are validated, a case-finding approach is appropriate.

Other techniques for assessing skeletal status have been less well validated than absorptiometric techniques, but quantitative ultrasound and computed tomography are helpful in the assessment of fracture risk. The T-score cannot be used interchangeably. All risk assessments, whatever the method used, should permit an assessment of absolute risk of fracture.

BMD measurements may also be used to monitor response to treatment or compliance with treatment, but their optimal use for this purpose requires further research.

Biochemical indices for skeletal turnover may be useful in risk assessment, but further research is needed to determine their value in clinical practice to monitor treatment.

Assessment of individuals with suspected osteoporosis should include the measurement of BMD where available and indicated (see below). Other factors to consider in assessment are the differential diagnosis, the cause of the osteoporosis, and the management of any associated morbidity. Recommendations are included for the routine investigation of patients with osteoporosis.

Bone densitometry is recommended in the presence of:

- radiographic evidence of osteopenia and/or vertebral deformity;
- loss of height, thoracic kyphosis (after radiographic confirmation of vertebral deformity);
- previous low-trauma fragility fracture;
- prolonged therapy with corticosteroids (e.g. prednisolone at 7.5mg daily for 6 months);

- premature menopause (age <45 years);
- prolonged secondary amenorrhoea (>1 year);
- primary or secondary hypogonadism;
- chronic disorders associated with osteoporosis;
- a maternal history of hip fracture;
- a low BMI.

Men and women with BMD values 2.5 standard deviations or more below the average for the young healthy female population (i.e. osteoporosis) should be offered appropriate intervention. Intervention can also be offered to individuals with osteopenia who have strong risk factors that increase their risk of fracture.

The use of BMD assessment to target treatment in this way costs less per fracture averted than treatments given on a basis of risk factors alone. Although this strategy is not applicable to all individuals and is therefore conservative, it is justified from a health economics perspective. To overcome these limitations, further research on optimizing a case-finding strategy is recommended.

8.4 Prevention and treatment of osteoporosis

Many interventions may reduce the number of osteoporotic fractures, but not all have been rigorously evaluated. Interventions for which there is broad support, based on observational data or randomized trials with surrogate end-points, include:

- the provision of a balanced diet which prevents low body weight throughout life and provides a calcium intake equal to the recommended dietary allowance (generally < 800mg daily) from late childhood;
- encouragement of a physically active lifestyle;
- maintenance of eugonadism (in women until age 45–50 years);
- avoidance of smoking and of high alcohol intake;
- minimization of glucocorticoid use and consideration of prophylaxis against osteoporosis when such agents are used;
- promotion of vitamin D supplementation and/or adequate time spent outdoors (to permit endogenous synthesis of vitamin D) in the elderly;
- programmes aimed at preventing falls among the elderly, and use of hip protectors in those at very high risk of falls.

The menopause provides an opportunity for women to be counselled on the consequences of estrogen deficiency and on the benefits and risks associated with long-term HRT.

Interventions for which there is consistent evidence from randomized controlled trials of antifracture efficacy include supplementation with calcium and vitamin D in the elderly and treatment with bisphosphonates in postmenopausal women with osteoporosis. Selective estrogen receptor modulators also prevent vertebral fractures. There is less evidence for the beneficial effects of HRT and calcitonin on fracture risk. Inconsistent results from trials with fluorides preclude their widespread use in the treatment of osteoporosis at present.

In general pharmacological interventions are expensive and may have adverse effects; to be most cost-effective, they should therefore be targeted to those at highest risk of fracture. Current ability to predict fractures means that intervention is possible before fracture has occurred. It is, however, never too late to intervene in patients with osteoporosis.

8.5 Socioeconomic aspects

Osteoporosis and the fractures associated with it constitute a major public health concern. Hip fractures account for significant morbidity, disability, decreased quality of life, and mortality. The adverse effects of vertebral and forearm fractures on most of the activities of daily living are also significant, although not as great as those of hip fracture. The cost of care is high and the implications for public health expenditure are serious. In both developed and developing countries, osteoporosis will become a major burden as the population ages.

Socioeconomic evaluation of osteoporosis can be undertaken to estimate the cost of disease, the effectiveness of treatments, and the effects of strategies to identify patients at high risk such as screening and case-finding, or to assess global strategies. The costs of osteoporosis can be divided into direct (fracture-related) and indirect costs. The indirect costs depend on a number of assumptions, and in particular on the impact of working definitions of osteoporosis based on bone density threshold and on indices of vertebral fracture. The indirect costs of osteoporosis require further investigation.

The costs of osteoporosis are considerable and are comparable with those of many other chronic disorders in women including breast cancer, arthritis, diabetes and chronic obstructive pulmonary disease. Hip fracture accounts for more than half of all direct costs.

The usefulness of screening the general population by means of BMD has been the subject of much discussion. The case for screening

women by measuring BMD at the time of the menopause is weak, inter alia, because of the performance characteristics of densitometry, the low absolute risk of fracture at this time and the poor continuance of treatments. The case is stronger in older individuals because the absolute risk of fracture is higher and because clinical risk factors are more common. Such factors can be used to enhance the performance of densitometry, but a screening strategy in the elderly has yet to be developed and tested.

In the absence of screening, a case-finding strategy is advocated. The use of risk factors to direct further assessment with densitometry gives a cost-benefit ratio greater than that obtained with each clinical factor alone.

Treatments for osteoporosis can be cost-effective provided that patients are at sufficiently high risk of fracture. Important determinants of cost-effectiveness include age, clinical risk factors, costs of intervention and the offset of therapeutic activity once treatment is stopped.

Global strategies aimed at increasing the BMD of the general population have not been adequately tested, but general advice on lifestyle is an important component of patient care.

8.6 Delivery of care and education

Proper provision for osteoporosis requires a clearly defined structure, sufficient facilities with provision for the reimbursement of costs, effective guidelines, and mechanisms for monitoring the system.

A shared approach involving both primary care and specialist facilities will ensure an integrated approach to the care of patients with osteoporosis. A local strategy for osteoporosis care and proper organization of health professionals within a district should be developed by local osteoporosis planning and coordinating teams, based on national and international consensus. Concerted action in each country should be coordinated by an appropriately skilled and experienced national osteoporosis planning and coordinating group, which should be responsible for launching a comprehensive national osteoporosis programme.

Facilities for the diagnosis and treatment of osteoporosis are inadequate in many countries. This applies particularly to the availability of bone densitometry systems. In some parts of the world, the number of hospital beds dedicated to patients with hip and certain other fractures is not sufficient to meet the expected increase in the number of fractures. Apart from the shortage of densitometry equipment and

hospital beds, there are still too few specialists with adequate expertise in bone diseases.

Reimbursement of the cost of bone densitometry measurements is not available, partial or restricted in many countries, thus limiting the use of this procedure even where resources are available. Reimbursement of effective bone-active agents varies from 0% to 100% depending on the country.

Comprehensive and useful international guidelines on osteoporosis have been developed and published. However, guidelines should always be adapted and distributed by local osteoporosis teams taking into account characteristics of the population and osteoporosis care in the area concerned. In addition to setting up a system to deliver care to patients, it is also essential to monitor effectiveness and the appropriate use of diagnostic tools, and implement quality control.

Ignorance about osteoporosis is still common among health professionals, patients and the public, so that the education of all of these groups is necessary. The aim should be to increase knowledge of bone physiology and osteoporosis, raise the awareness of major risk factors, and provide information on possibilities of primary and secondary prevention and the management of the disease. Patient compliance can be increased by using effective methods of patient education and individualizing education in a stepwise manner.

9. Recommendations

The scientific group made the following recommendations:

1. The general population should:
 - maintain a physically active lifestyle with adequate exposure to sunlight; this applies particularly to the elderly in extreme latitudes;
 - avoid smoking and high alcohol intakes;
 - ensure that dietary intake of calcium is that recommended for the country or region concerned;
 - maintain an appropriate body weight.
2. International agencies should:
 - Provide accurate Web-based information that is available worldwide.
3. Physicians should:
 - consider a diagnosis of osteoporosis in individuals with a fragility fracture;
 - remember that the prevention of osteoporosis begins with the acquisition of optimal bone mass during growth. Anything hindering the acquisition of bone mass such as malnutrition, should be identified and dealt with during childhood;
 - address known factors that stimulate bone resorption or inhibit bone formation, including hypogonadism, primary hyperparathyroidism, hyperthyroidism and hypercortisolism;
 - make use of bone densitometry, where available, for defined indications as mentioned in this report;
 - remember that the diagnostic threshold is not necessarily an intervention threshold. Whereas all patients with osteoporosis should be offered appropriate treatment, this can also be given to individuals who have osteopenia and important risk factors that contribute to fracture risk;
 - consider vitamin D and calcium supplementation in the elderly and in other high-risk groups;
 - develop programmes aimed at preventing falls among the elderly. Hip protectors should be considered for those at very high risk;
 - minimize glucocorticoid use and consider prophylaxis against osteoporosis when these drugs are used.
4. Health authorities should:
 - use BMD in a case-finding approach in which individuals are identified by the presence of one or more strong risk factors, since universal screening of asymptomatic postmenopausal women has not been shown to be cost-effective at present;

- facilitate access to bone densitometry and other methods of risk assessment for individuals at risk of osteoporosis to allow appropriate targeting of therapies, ensure that staff are properly trained and that the systems and technical procedures are subject to quality control;
 - consider reducing the risk of fracture by environmental measures such as enriching widely used foods with calcium, vitamin D, or both if necessary;
 - take into account the WHO *Guidelines for preclinical evaluation and clinical trials in osteoporosis*^a when considering the approval of new drugs for osteoporosis;
 - support the comprehensive education of health professionals, including general practitioners, in the management of osteoporosis;
 - support patient education and the establishment of self-help groups regionally and locally, and raise awareness of risk factors for osteoporosis and prevention strategies;
 - support national osteoporosis programmes instituted in association with the WHO and with other national and international organizations;
 - encourage the development of a subspecialty or specialty of metabolic bone disease.
5. Research should be carried out on:
- fundamental aspects of bone biology, taking into account progress in molecular genetics;
 - factors influencing the acquisition of bone mass during growth and bone loss during adult life in different countries, as shown by well designed clinical investigations;
 - the evaluation of biochemical markers of bone turnover in clinical practice;
 - the development of cheap diagnostic tools for osteoporosis and their assessment in monitoring treatment;
 - the development of risk-based guidelines for assessment that are relevant to men and women worldwide;
 - the development of agents to stimulate bone formation;
 - the effects of lifestyle and dietary interventions on fracture risk, as shown by feasibility studies and clinical trials;
 - the effectiveness of combination therapies and comparisons between therapies, as shown by controlled trials;
 - patterns of fracture and epidemiology in various parts of the world;

^a *Guidelines for preclinical evaluation and clinical trials in osteoporosis*. Geneva, World Health Organization, 1998.

- the development of inexpensive strategies for the prevention of osteoporosis suitable for use in developing countries;
- the measurement of the global burden of osteoporosis, using methods that permit comparisons with other chronic disorders.

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Annex

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Keep fit for life: meeting the nutritional needs of older persons.

2002 (viii + 119 pages)

Further information on these and other WHO publications can be obtained from Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland.

Bone is hard tissue that is in a constant state of flux, being built up by bone-forming cells called osteoblasts while also being broken down or resorbed by cells known as osteoclasts. During childhood and adolescence, bone formation is dominant; bone length and girth increase with age, ending at early adulthood when peak bone mass is attained. Males generally exhibit a longer growth period, resulting in bones of greater size and overall strength. In males after the age of 20, bone resorption becomes predominant, and bone mineral content declines about 4% per decade. Females tend to maintain peak mineral content until menopause, after which time it declines about 15% per decade.

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist. Osteoporosis occurs primarily as a result of normal ageing, but can arise as a result of impaired development of peak bone mass (e.g. due to delayed puberty or undernutrition) or excessive bone loss during adulthood (e.g. due to estrogen deficiency in women, undernutrition, or corticosteroid use).

Osteoporosis-induced fractures cause a great burden to society. Hip fractures are the most serious, as they nearly always result in hospitalization, are fatal about 20% of the time, and produce permanent disability about half the time. Fracture rates increase rapidly with age and the lifetime risk of fracture in 50 year-old women is about 40%, similar to that for coronary heart disease. In 1990, there were 1.7 million hip fractures alone worldwide; with changes in population demographics, this figure is expected to rise to 6 million by 2050.

To help describe the nature and consequences of osteoporosis, as well as strategies for its prevention and management, a WHO Scientific Group meeting of international experts was held in Geneva, which resulted in this technical report. This monograph describes in detail normal bone development and the causes and risk factors for developing osteoporosis. The burden of osteoporosis is characterized in terms of mortality, morbidity, and economic costs. Methods for its prevention and treatment are discussed in detail for both pharmacological and non-pharmacological approaches. For each approach, the strength of the scientific evidence is presented. The report also provides cost-analysis information for potential interventions, and discusses important aspects of developing national policies to deal with osteoporosis. Recommendations are made to the general population, care providers, health administrators, and researchers. Lastly, national organizations and support groups are listed by country.

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