Osteoporosis 2000–2010

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Historical background

The importance of osteoporosis has become more clear after the recognition that most hip fractures are caused by osteoporosis. This has caused interest and created financial possibilities for research on the pathophysiology and prevention of osteoporosis. The development of techniques for the assessment of bone mineral density has simplified diagnosis. The discovery that oestrogens could prevent postmenopausal bone loss and decrease the number of fractures has led to the conclusion that osteoporosis is not merely an inevitable consequence of aging but that prevention is feasible.

Current situation

Epidemiology

Data have become available on the worldwide incidence of hip fractures. The lifetime risk for hip fracture in a 50 year old woman is about 15% and in a 50 year old man 6%.[1] The incidence of hip fractures is steadily rising in the western world due to the increasing life expectancy and the progressive loss of bone in the femoral neck with aging.[2] The increase of hip fracture incidence is much steeper in Asian countries. The age-adjusted incidence of hip fractures has also increased in many countries except for the USA, where it shows a plateau, while in some other countries the secular trend appears to continue. Hip fractures are more common in women than in men in most countries but the sex ratio may vary from 4:1 to 1:1.[3] The incidence difference between various countries is much greater than the sex difference pointing to other causes than oestrogen deficiency (Figure 1). Studies on the prevalence and incidence of vertebral fractures suggest that vertebral deformities are not as rare in men as previously thought. The lifetime risk for vertebral fractures is about 15% in a woman of 50 years and about 6% in a man of 50 years.[1] Only about one in three vertebral fractures comes to clinical attention but part of the subclinical fractures may become clinical when a careful history is obtained.

Osteoporotic fractures are associated with significant excess mortality, morbidity and economic cost.[4] The survival rate 5 years following hip and vertebral fractures is around 80% of that expected for people of the same age without fractures.[5] Hip fracture mortality is higher for men than for women, increases with age, and is greater for those with co-existing illnesses and poor pre-fracture functional status. The interaction of acute injury or surgery with comorbid conditions, which are more common in men, may contribute substantially to the early excess mortality associated with this fracture. Excess mortality after verte-

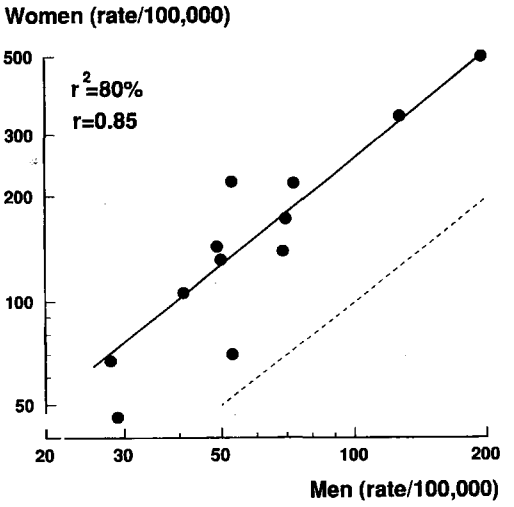

Figure 1. Relationship between the age-standardized rates of hip fracture for men and women in Europe. At the bottom left is Poland, at the top right is Sweden (reproduced with permission from Johnell et al., ref. 3).

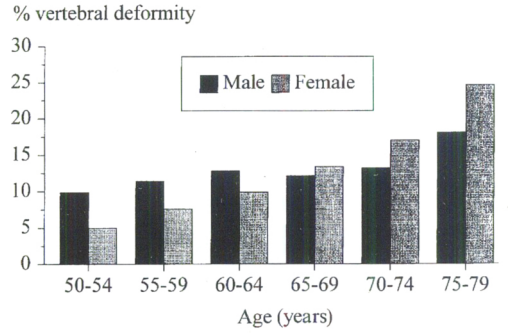

Figure 2. Age- and sex-specific prevalence of vertebral deformity: results from the European Vertebral Osteoporosis Study (reproduced with permission from Silman and O'Neill, Osteoporosis 1996, Excerpta Med. Int. Congress Series 1118, p. 91).

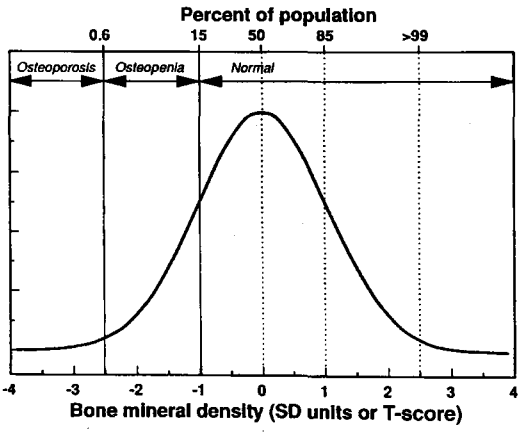

Figure 3. Distribution of bone mineral density in young adult women and definition of osteopenia and osteoporosis (reproduced with permission from Kanis et al., ref. 18).

bral fracture appears to increase progressively after diagnosis of the fracture. Impaired survival is more pronounced for vertebral fractures that occur secondary to mild/moderate trauma than for those associated with severe trauma. Survival at 5 years again appears to be less for men than for women. In the United States, osteoporotic fractures contribute substantially to the two million person-years of functional impairment and $45 billion in direct medical costs which are attributable to osteoporosis over the next decade.[6]

Despite the recognition of thoracolumbar spine fractures since antiquity, our understanding of their epidemiology has remained scanty for two reasons: (1) a significant proportion of vertebral fractures are asymptomatic, and radiographic surveys of the general population are required to generate valid estimates of prevalence; and (2) there has been difficulty in achieving consensus as to the definition of vertebral deformities from lateral thoracolumbar radiographs.[7] Research into this area has a particular urgency as vertebral deformities remain the major clinical means whereby patients with osteoporosis are identified, and therapeutic regimens commenced with the aim of reducing the future risk of other osteoporotic fractures. The recent use of morphometric and semi-quantitative visual techniques for grading vertebral deformation in large epidemiological studies throughout Europe has permitted better description of the epidemiology of prevalent and incident deformities. In the European Vertebral Osteoporosis Study (EVOS), 15,570 men and women aged 50-79 years were selected from population registers in 36 European centres.[8] Lateral spine radiographs were taken according to a standardised protocol and evaluated centrally. The overall prevalence of morphometrically defined vertebral deformity was 12% in men and women. The prevalence increased with age in both sexes but the gradient was steeper among women than men (Figure 2). Thus, the frequency of deformities in men aged 50–54 years was around 10%, rising to 18% at age 75–79 years. These estimates were derived using the McCloskey/Kanis algorithm for definition of deformities, and are somewhat lower than those obtained using the Eastell/ Melton classification. There was substantial geographic variation, with the highest rates observed in Scandinavian countries. However, ecological associations could only be detected with physical activity level and body mass index.

Bone mineral density

The measurement of bone mineral density (BMD) has become the main diagnostic method for osteoporosis. BMD can be easily measured by dual X-ray absorptiometry with very low radiation exposure. Fracture risk increases exponentially with a linear decrease of BMD.[9] The World Health Organization has accepted a definition of osteoporosis based on BMD measurements.[10] This definition is based on T-score, i.e. the BMD of an individual minus the mean BMD of young adult women (peak bone density) expressed in standard deviations (SD). A T-score lower than -1 (one SD below peak bone mass) indicates low bone mass (osteopenia). A T-score lower than -2.5 indicates osteoporosis (Figure 3). A T-score lower than -2.5 accompanied by fractures is defined severe osteoporosis. BMD may be measured at the lumbar spine, the hip or a peripheral region of interest such as the radius or the calcaneus (Figure 4). Risk prediction for hip fracture is better when BMD is measured at the hipHowever, T-scores at various regions may be very different in one patient. Reference values, thus T-scores, may vary with the type and brand of bone densitometer as each manufacturer distributes its own

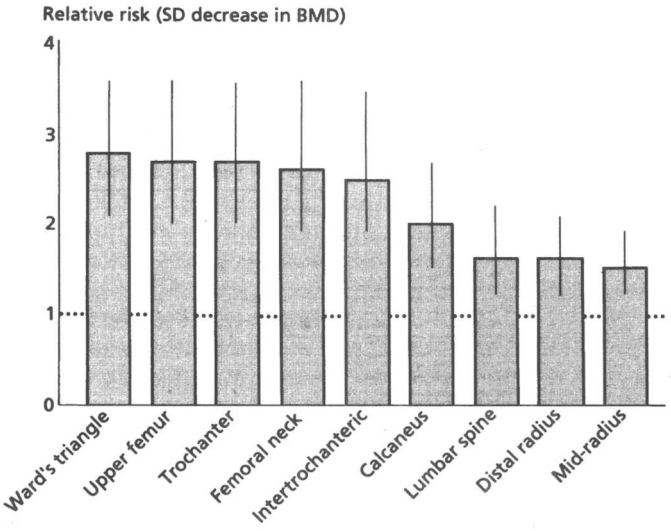

Figure 4. Age-adjusted relative risk for hip fracture (±95% confidence intervals) for each standard deviation decrease in bone mineral density at various sites of the skeleton (reproduced with permission from J Kanis, Osteoporosis, Blackwell Science, London 1994).

reference values.[11-13] This creates the possibility that a patient may be classified as osteoporotic in one clinic and non-osteoporotic in another clinic according to the region of interest measured and the type of bone densitometer used.[11,12] The results of large epidemiologic studies in a population sample may not agree with reference values distributed by the manufacturer.

Risk assessment

Risk factors such as early menopause, previous disease, smoking or medication are of little value to predict low BMD.[14] However, large epidemiological studies have made it clear that some risk factors may predict fractures independently of BMD. Recent data have also become available on the relationship between vertebral deformity and the risk of other age-related fractures. Previous vertebral deformities have been shown to increase the risk of subsequent vertebral deformities by 7–10 fold.[15] A similar increase in risk has been observed for second hip fractures among men and women who have already sustained their first hip fractures. In contrast, the risk of hip fracture among elderly men and women who have sustained distal forearm fractures is only doubled.[16] In a population-based retrospective cohort study in Rochester, Minnesota, 691 Rochester residents <70 years of age who were radiologically diagnosed for the first time with one or more vertebral deformities over the period 1950–1989, were followed for the development of subsequent limb fractures.[17] Over 8,342 person-years of follow-up, 58 subjects were identified with a first incident hip fracture, 48 with new forearm fractures, and 71 with proximal humeral fractures. The standardised morbidity ratios of observed to expected fractures were 1.7 (95% CI 1.3–2.2) for the hip, 1.4 (95% CI 1.0–1.8) for any limb fracture. The increased risk was apparent among men and women and was more marked in subjects with vertebral deformities associated with moderate or minimal trauma, than in those whose fractures were due to severe trauma. These data suggest that the risk of hip fracture among men and women who sustain a clinically diagnosed vertebral fracture is somewhat smaller than the previously reported risk increase for additional vertebral deformities. However, the predictive capacity of previous low trauma fragility fractures remains sufficient to their cost-effective use in any therapeutic algorithm which aims to prevent future hip fractures.[18]

Family history (e.g. maternal hip fracture) also increases the risk for fracture hip fracture irrespectively of BMD. Other risk factors which provide an indication for BMD measurement or may be used in addition to it, are oestrogen deficiency, hypogonadism, corticosteroid therapy, low body mass, malabsorption, (past) hyperthyroidism and immobility.[19]

The risk of vertebral deformity among men in the EVOS Study was significantly elevated in those with very high levels of physical activity,[20] suggesting the aetiological importance of trauma. In contrast, women with higher levels of customary physical activity had a reduced risk of deformity. Risk was elevated

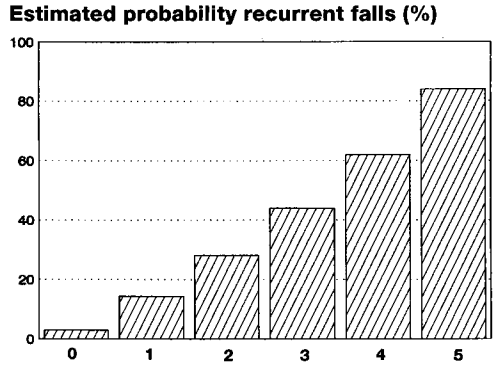

Figure 5. Estimated probability of recurrent falls (2 or more) during a 28-week period in 354 elderly in homes or aparments for the elderly in Amsterdam according to the presence of risk factors. 1 = immobility, 2 = 1 + poor mental state, 3 = 2 + orthostatic hypotension, 4 = 3 + dizziness, and 5 = 4 + stroke (reproduced with permission from Graafmans et al., ref. 25).

among women in the highest quintile of menarche (OR = 1.5; 95% CI 1.2–1.9), and reduced among those with later menopause (OR = 0.8; 95% CI 0.6–1.0), and those who had used the oral contraceptive pill (OR = 0.8; 95% CI 0.6–1.0).[21] Other risk factors for vertebral deformity included a maternal history of hip fracture and low body mass index. There was a strong association in these studies between the number of vertebral deformities and height loss and the reported prevalence of back pain in the year prior to interview.[22]

Biochemical markers of bone resorption and bone formation can be measured in blood or urine samples. Examples are the serum osteocalcin concentration for bone formation and urine deoxypyridinoline excretion for collagen breakdown, i.e. bone resorption. These bone turnover markers may indicate the rate of bone loss that will occur. However, the prediction of the decrease of BMD by bone turnover markers is not very good. In the French EPIDOS study a marker of bone resorption predicted hip fracture risk independently of BMD.[23]

Risk assessment in the elderly should be completed with estimation of the fall risk[19,24] (Figure 5). Strong risk factors for falls are impaired mobility, stroke, postural hypotension, visual disturbance, cognitive impairment and medication.[25] A risk stratification may be based on the use of risk factors, a BMD measurement and a biochemical measurement.

Prevention and treatment

The aim of prevention and treatment is to prevent the occurrence of (further) fractures. The prevention in patients who have already suffered one or more fragility fractures is also called tertiary prevention. Treatment also includes the alleviation of complaints caused by the fractures. The latter involves physical therapy, improving coordination, balance and mobility, pain medication and sometimes the use of back supports.[26] The patient should receive nutritional advice and identified causes of osteoporosis should be treated. Prevention has been focused at adolescents, women around menopause, and elderly people. Special circumstances include prevention of osteoporosis due to corticosteroids or to disuse. Calcium and physical activity increase BMD in adolescents and this effect, although small, may last for decades. Bone loss around menopause can be prevented by oestrogens. Bone loss restarts when oestrogen therapy is discontinued and the positive effects of therapy disappear in subsequent years. There is evidence from epidemiological studies that oestrogens can prevent fractures of the radius, hip and vertebrae.[27] When oestrogens are combined with progestagens, the risk for endometrial cancer is not increased. Oestrogen therapy should be prescribed for at least 8 or 10 years, but the longer the use the greater the risk for the development of breast cancer.[28] Calcium supplementation has a positive effect on BMD before menopause and several years after menopause but not in the perimenopausal period.[29,30] There is some evidence that calcium may prevent vertebral fractures.[31] Vitamin D supplementation corrects vitamin D deficiency which is common in elderly people, suppresses secondary hyperparathyroidism and increases BMD in the femoral neck.[32] In a study in France, supplementation with vitamin D_3 800 IU/day and calcium 1200 mg/day decreased the incidence of hip fractures and other peripheral fractures in nursing home residents who were vitamin D deficient and had a low calcium intake.[33] In contrast, supplementation with vitamin D_3 400 IU/day in a mixed population of elderly in Amsterdam increased BMD of the femoral neck but did not decrease the incidence of hip fractures.[34] Bisphosphonates inhibit bone resorption and increase BMD in the lumbar spine, the hip and to a lesser degree in the radius.It has been demonstrated that cyclical etidronate with calcium decreases the incidence of new vertebral fractures.[35] In a double blind trial in 2027 women, alendronate treatment decreased the incidence of vertebral hip, and radius fractures.[36] Bisphosphonates also can prevent postmenopausal bone loss and bone loss following corticosteroid treatment.[37,38] Currently, promising drugs which inhibit bone resorption are oestrogen agonists such as raloxifene,[39] and drugs which stimulate bone formation such as synthetic parathyroid hormone.[40] Another approach is to influence the impact of falls in the elderly by using

hip protectors. It has been demonstrated that hip protectors decrease the number of hip fractures in institutionalized elderly.[41]

Future

Epidemiology

The number of osteoporotic fractures will increase in most countries because of the increasing number of elderly people. The increase will be faster in Asia, Africa and Oceania. The age-adjusted incidence of hip fractures is still increasing in several countries.[14] This may be due to a decrease of bone quality or survival of the less fit. As a consequence the cost of acute care for osteoporotic patients will increase. These increasing costs have to be balanced against the costs of screening and preventive treatment for osteoporosis.

Diagnosis

Whereas diagnostic criteria have been established by the WHO, there is no uniformity in bone densitometry.[11-13] It is urgent that manufacturers of DXA equipment standardize their machines so that every machine gives the same result in one patient. The reference values should be obtained from large population studies such as NHANES in the USA and EVOS in Europe and should be adapted for region or country.

Another goal is the further development of ultrasound as a screening method for osteoporosis risk.[42] Ultrasound may be particularly suitable to assess the risk for hip fracture in elderly people, as the equipment is free of radiation and portable so that it can be used everywhere. Ultrasound measurements in the heel can predict hip fracture almost as well as DXA.[43]

Risk assessment

The risk factor approach should be further developed. The accumulation of risk by combination of risk factors and tests (BMD, ultrasound, biochemistry) should be further investigated.[19,23] An alternative approach for risk assessment could be a decision tree. Novel risk factors to be investigated are genetic factors such as the vitamin D receptor gene[44] or collagen IA1 gene[45] and low body weight during infancy.[46]

The assessment of risk factors for falls in the elderly should be further developed. Assessment of bone density in the elderly whether by DXA or by ultrasound should be accompanied by evaluation of fall risk.[14]

Screening

Screening of perimenopausal women by measuring BMD is controversial because it probably is not cost-effective. A working group of the WHO has proposed screening at an age of 65–70 years, closer to the age when most fractures occur.[10] This may be cost-effective, as the overall fracture risk is higher and adequate preventative treatment is available. Pilot screening projects might be started in this age group. Another approach is to screen clearly defined risk groups, such as patients who already experienced a fragility fracture and patients who are using corticosteroids for more than 2-3 months. The risk for hip fracture is particularly high in institutionalized elderly.[47] A focused program in these groups could be highly effective.

Prevention and treatment

Oestrogen therapy is well able to decrease bone resorption and arrest bone loss in postmenopausal women. However, the risk for breast cancer increases with the exposure time. Very recently the oestrogen-agonist raloxifene has been approved for treatment of post-menopausal osteoporosis.[39] Oestrogen-agonists such as raloxifene do not increase and may even diminish the risk for endometrial and breast cancer. The place of these oestrogen-agonists should be further defined.

Oestrogens decrease bone resorption and lead to a small increase of BMD due to filling up of resorption spaces, but restoration of the trabecular network will not occur. In patients with vertebral fractures, the progress of osteoporosis may be slowed down but not reversed because BMD and bone architecture cannot be restored to the premorbid state. The same probably applies to the use of bisphosphonates. There is an urgent need for drugs which stimulate bone formation such as synthetic parathyroid hormone, growth factors such as insulin-like growth factor 1 and maybe anabolic-type drugs.[40] Calcium and vitamin D can prevent fractures in institutionalized elderly, when they are vitamin D deficient and their calcium intake is low, but the prophylactic use in other groups of elderly people should be further investigated. Two problems should be resolved. Currently, only a small proportion of osteoporotic patients is treated, and many patients are only treated for a short time period. The latter issue is important, as the effect of most drugs used for osteoporosis will diminish soon after discontinuation of the drug.

When defined according to WHO criteria, osteoporosis is present in about 50% of all elderly above 80 years.[18] As there will be budget constraints, the risk groups for osteoporotic fractures who will need long term treatment, should be clearly delineated . Many patients may have to be treated for one or two decades. A long-term strategy employing several drugs in sequence should be developed (Figure 6).[47]

The place of exercise in the treatment of osteoporo-

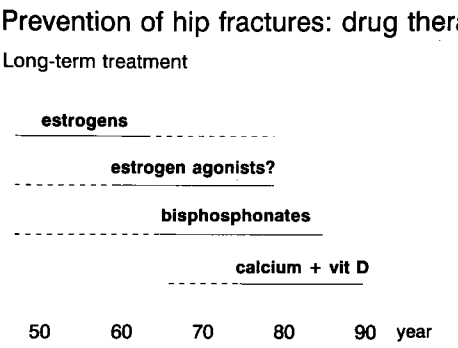

Figure 6. Long-term strategy for sequential use of drugs in the treatment of osteoporosis.

sis is not well defined. Exercise may be very useful to improve balance and coordination and decrease fall risk, but data are scanty.[48] It has been shown that hip protectors can prevent hip fractures in the institutionalized, but again the candidates for hip protectors should be further defined.[41] Non-compliance is another problem associated with hip protectors as well as with many drugs.

Public health issues

The health care budget for osteoporosis will be under increasing pressure. The financial resources should be used in the most efficient way. Treatment should be targeted at those who need it most urgently. Various treatments for different groups should be compared by cost-effectiveness studies. Outcomes in such studies should be fracture and quality of life.[49] Nutrition is another public health issue. Vitamin D supplementation in the elderly can be realized by adding vitamin D_3 to milk, which ensures adequate calcium intake as well. Whereas many diagnostic and therapeutic methods have become available in the last decades, they have not yet been implemented. This should be a general aim for the next decade.

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