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LESSONS FROM A SYMPOSIUM ON OSTEOPOROSIS HELD IN THE COLLEGE ON 17 APRIL 1996*

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The impact of osteoporosis on public health and NHS resources is considerable. In this symposium on osteoporosis which attracted participation by physicians and paramedical staff from a broad range of disciplines, a range of issues relevant to the epidemiology, prevention, diagnosis and treatment of this important condition were addressed. Some of the principal messages which struck this reviewer are outlined below.

Extent of the problem

Osteoporosis can be defined as a reduction in bone mass and disruption of bone architecture leading to increased bone fragility and increased risk of fracture. Using the World Health Organisation (WHO) definition of osteoporosis (bone mineral density (BMD) > 2.5 SD below that of a premenopausal woman), the prevalence of osteoporosis in postmenopausal women in the UK is estimated to be 25%. The close relationship that exists between low BMD and increased susceptibility to fracture means that the relative risk of pathological fracture increases by 20-30% for each standard deviation reduction in BMD from the mean: thus for a fifty year old woman the estimated lifetime fracture risk is 30%, equivalent to the risk of developing coronary artery disease. The incidence of such fractures, which typically occur in the bones at the wrist, hip and spinal column, increases with age in women, and the associated morbidity - pain, immobilisation, loss of height, spinal deformity - is considerable. The incidence of hip and spinal fractures in men also increases with age, though the incidence of male wrist fractures remains constant throughout life.

The financial cost of osteoporotic fractures (estimated at £750M per annum) is principally attributable to fractures of the head of femur. Sixty thousand women in the UK suffer femoral fractures annually with a peak incidence at seventy-nine years and a six month mortality of up to 20%. Of those who survive, 30% become totally dependent, the majority requiring institutional care. Importantly, the incidence of hip fracture in Europe is projected to double over the next five decades with an even greater increase in Asia. Clearly if these projections are realised there will be major public health and financial implications. Possible contributory factors to this escalation include increased life expectancy, physical inactivity, dietary changes and increasing alcohol consumption influencing falls, and changes in bone mineral density and mechanical strength; geometric changes in the femoral neck may also be relevant.

The epidemiology of vertebral fractures is less clear due to differences in populations studied and diagnostic criteria used. However it has been estimated that forty thousand women in the UK suffer a vertebral fracture annually though only one third come to medical attention, possibly because thoracic kyphosis and loss of height due to vertebral osteoporotic collapse are misinterpreted as consequences of normal ageing. Prevalence studies in the UK report a vertebral fracture in 7.8% of women

* A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* vol 26 p. 518

aged 48-81 years as compared with a North American study which found a vertebral fracture in 26.3% of women aged 65-70 years.

Diagnosis and assessment

Bone mass peaks in early adulthood and declines thereafter with accelerated bone loss in females for 5-10 years after the menopause. The rate of loss of BMD in women however varies at different sites with spinal trabecular loss being greatest at the menopause. In contrast, hip BMD falls with advancing age in both sexes and appears to be predominantly age-related rather than hormone-dependant. Spinal BMD also falls with age in men.

Criteria for the diagnosis of osteoporosis are contentious. Using WHO definitions, 50% of healthy 70 year old females would be classified as osteoporotic and 80% as osteopenic (BMD > 1.0 and < 2.5 SD below that of a premenopausal woman). The application of disease labels based on normal reference ranges in the absence of clinical problems may cause difficulty, and the indiscriminate use of dual energy X-ray absorptiometry (DEXA) scanning to assess bone mineral content or density may lead to the diagnosis of osteoporosis in asymptomatic women who may never develop complications. Ideally preventive treatment should be targeted at those patients who are more likely to develop complications of osteoporosis, and the diagnostic challenge is to be able to identify this cohort. The concept of a 'fracture threshold' in BMD was put forward with the implication that patients who fall below this level should be considered for treatment of osteoporosis even in the absence of complications. Although there is a strong relationship between BMD and fracture risk (and in women between low BMD and mortality unrelated to fracture), no BMD exists above which fractures do not occur and vice versa. As an alternative, some have advocated defining osteoporosis as either a reduction in BMD sufficient to cause fracture, or reduction in BMD as compared to age-and sex-matched controls.

Genetic influences

Genetic factors exert an important influence on bone mineral density throughout life, and it has been estimated that 75-85% of variance in BMD between individuals can be determined by genetic influences. This follows observational studies which have shown greater concordance in BMD between identical as compared with non-identical twins, low BMD in the daughters of osteoporotic women, and a family history of osteoporosis predicting low BMD.

A large number of potential candidate genes was suggested for osteoporosis. Three common polymorphisms for the vitamin D receptor have been described and twin studies have suggested that allelic variants in this gene may predict BMD. The strength, and the very existence of this genetic determinant is however very controversial; its effects may also be modified by calcium intake particularly in relation to osteoporosis at the femoral neck. Three polymorphisms for oestrogen receptor genes have also been described and these, along with the collagen type I gene may also contribute in determining bone mass.

Osteoporosis prevention in the peri-menopausal patient

Peak bone mass in early adulthood is an important predictor of postmenopausal BMD and therefore also of fracture risk; previous fracture, age at the menopause and a family history of hip fracture are other independent risk factors. The prevention of

osteoporosis in the peri-menopausal patient should therefore ideally start some years prior to the menopause with measures to optimise peak bone mass. Adequate dietary calcium during childhood is important: twin studies have indeed demonstrated a significant improvement in BMD following calcium supplementation to girls under the age of eleven years. Regular exercise also influences bone mass and high level of physical activity lifelong is associated with increased BMD. The effects of strength training and aerobic exercise may be synergistic though it is likely that such exercise needs to be sustained throughout life for its benefit to be maintained. Other life-style adaptations such as stopping smoking and moderating alcohol intake are also relevant.

Bone loss however is maximal during the peri-menopausal period, defined as the time between having regular menses and their complete cessation, and women who experience menopausal symptoms are at greater risk of developing osteoporosis than asymptomatic women. Physical inactivity and deficiencies of calcium and vitamin D contribute to peri-menopausal bone loss although calcium supplementation around the menopause does not significantly influence the degree of bone loss. Oestrogen deficiency however has a major influence on peri-menopausal bone loss and hormone replacement therapy, whether administered orally or percutaneously, is effective in retarding bone loss - in addition to having positive effects on cardiovascular health. Exercise has an additive effect with oestrogen therapy on BMD. Oestrogen supplementation during the early peri-menopausal period may lead to problems associated with the superimposition of exogenous oestrogen on the endogenous cycle. If hormone replacement therapy is poorly tolerated, biphosphonates should be considered.

Is screening for osteoporosis worthwhile?

The effectiveness of a screening programme for osteoporosis depends on the sensitivity of the screening test used, the efficacy of, and long-term compliance with, any suggested intervention, and the rate of screening uptake. The current public health burden of osteoporosis could suggest that screening by DEXA should be considered, especially as effective treatment is now available which can reduce fracture risk. The perceived advantages of screening in terms of fractures prevented need to be set against the costs involved and the requirement to allocate limited financial resources most effectively. Cost-effective screening requires the optimisation of screening slots available, and a new recruitment method combining open invitations with confirmable reminders was recently shown to achieve more efficient slot coverage than the existing fixed appointment system. In further support of screening for osteoporosis is the finding that those women who fail to attend for screening are at relatively low risk of low BMD. Treatment compliance with hormone replacement therapy (HRT) is also improved if women with low BMD are made aware of the result of the screening. Population screening of peri-menopausal women is unlikely to reduce the overall fracture burden and population screening of the elderly may therefore be more cost-effective.

Male osteoporosis

Bone loss in men, as in women, increases with advancing age and is associated with an increase in the age-specific incidence of fractures of the hip and spinal column though not of the forearm. The aetiology of male osteoporosis is often multifactorial and several contributing causes can be found in the majority of patients. Peak bone mass, an important determinant of bone mass in later life, may be influenced by

genetic factors although there appears to be no relationship between vitamin D receptor polymorphisms and male osteoporosis. Hormonal influences are particularly important around puberty and men with delayed puberty have reduced spinal BMD.

Hypogonadism, often not apparent clinically, is found in more than 50% of elderly men presenting with hip fractures and 16% of males presenting with vertebral body crush fractures. The causes of bone loss in hypogonadal osteoporosis are uncertain but it is likely that increased bone resorption, reduction in bone mineralisation, low plasma vitamin D and deficiency in androgens and oestrogen are all involved. Genetic factors, cigarette smoking, alcohol consumption and physical inactivity are other important contributors to age-related bone loss in males.

The treatment of male osteoporosis remains controversial as no controlled studies have been conducted. Lifestyle modifications and the recognition of underlying secondary factors, particularly hypogonadism, are important. Testosterone administration has been demonstrated to improve spinal BMD in eugonadal men with primary osteoporosis as well as in men with hypogonadism. The role of bisphosphonates in male osteoporosis is less clear, though observational studies suggest that they may be associated with an increase in bone mineral density at the spine, and to a lesser extent the hip.

Can hip fracture be prevented?

The estimated lifetime risk of fracture of the proximal femur for a 50-year-old woman is 17.5%, and 6.0% for a man of the same age. With the projected doubling of hip fracture incidence over the next fifty years, it is estimated that there will be 6.26M hip fractures per annum worldwide by the year 2050. As the risk of hip fracture is inversely proportional to BMD, interventions which retard bone loss may result in a reduction of fracture incidence.

Recently the influence of parathyroid hormone (PTH) on bone mass has been reassessed following the observation that PTH is raised in those elderly patients who have sustained a hip fracture, compared to age and sex-matched controls. Secondary hyperparathyroidism may occur as a result of a fall in serum 25(OH) vitamin D that occurs with ageing. This may be due to decreased intake of vitamin D-containing food, reduced solar exposure and diminished cutaneous synthesis of vitamin D, as well as to a reduction in calcium intake and absorption. A three year study of supplemental vitamin D and calcium in elderly patients showed a reduction in hip fracture incidence by 25% and in all fractures by 18%; a rise in serum 25(OH) vitamin D and reduction in PTH was also noted. Supplemental vitamin D and calcium may therefore have a role in reducing hip fracture incidence in the elderly, particularly those in whom vitamin D deficiency is likely. HRT also reduces the risk of fracture in the elderly though the resumption of cyclical vaginal bleeding may be unacceptable for many women. The importance of non-pharmacological methods to reduce fracture risk such as hip protectors and appropriate visual and walking aids to reduce the risk of falls should not be overlooked.

The management of vertebral fractures

Bone undergoes constant remodelling through a balance of osteoblast and osteoclast activity; in many forms of osteoporosis, there is insufficient filling of osteoclast-generated resorption cavities by bone-forming osteoblasts. The drugs currently used to treat vertebral osteoporosis (oestrogens, biphosphonates and calcitonin) do so by inhibiting bone turnover. Oestrogen replacement in post-menopausal women

reduces bone loss and the risk of vertebral fracture, effects which persist for as long as treatment is given. Studies of alternative interventions however have given contradictory results which may perhaps reflect the lack of consensus on the definition of a vertebral fracture. Cyclical etidronate increases lumbar BMD for the first 2-3 years of treatment; thereafter, lumbar spine BMD remains steady or falls albeit at a slower rate as compared to placebo-treated patients. Fracture risk is reduced slightly during the first two years of treatment. Continuous treatment with alendronate has recently been shown to increase BMD and marginally reduce hip and spinal fracture rates following three years of therapy. Two or three years of treatment with bisphosphonates around the menopause may not however affect the incidence of vertebral or hip fractures in later life.

Cost-effectiveness of secondary prevention

Given limited resources, it is important to consider which of the available potential interventions are most cost-effective in the secondary prevention of osteoporosis and in order to do so one has to consider both the present-day, and future costs and benefits of a given treatment. The latter are translated into equivalent present-day costs by the process of discounting where one estimates the drawbacks associated with future costs and benefits e.g. delay, uncertainty of benefit. Using fracture incidence rates and estimated effectiveness of treatment and cost, different interventions can be compared. Screening peri-menopausal women for osteoporosis results in 460 discounted fractures per 100,000 women compared to approximately 1,300 discounted fractures if screening is performed at age 70. If one accepts that the incidence of hip fracture in Scotland is 2.3% and that the effectiveness of vitamin D in preventing hip fracture is 22%, using an economic model one could consider vitamin D to be the measure most cost-effective in reducing hip fracture incidence. More costly though possibly more effective interventions such as HRT, calcium and vitamin D combined, and bisphosphonates would have to be targeted at specific patient groups if they are also to be cost-effective.