Review article

THE MANAGEMENT OF OSTEOPOROSIS

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Osteoporosis has been defined as "a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk".¹ This is clearly demonstrated in Figure 1, with the diagram on the left showing normal bone with thick extensive plates of trabeculae, while on the right these plates are notably thinner with the central one in the process of fracturing. When osteoporotic bone is insufficiently strong to withstand normal day-to-day activities, the structure fails, and the resulting fracture is called an 'insufficiency' fracture.

Osteoporosis has been identified as an orthopaedic 'epidemic' because of the increased numbers of fractures of the hip and wrist which have been occurring since the 1970s (Fig. 2). There is, however, now evidence to suggest that the incidence of fractures of the hip may be levelling off. The insidious onset of osteoporosis usually lies undetected until it presents as a fracture after minor trauma and the condition is now seen both in the UK and worldwide as a major problem in health care. In the UK alone over 200 000 osteoporotic fractures are sustained each year, with over one-third of all adult women suffering a fracture related to osteoporosis in their lifetime.² Caucasian women in Europe now have a lifetime risk of sustaining a fracture of the hip of between 11% and 18%.³⁻⁵ The annual cost to the nation of fractures overall is over £942 million, with those of the hip responsible for 87% of this.⁶ This means that each primary care group will spend, on average, £681 340 in acute costs for these insufficiency fractures and £1 439 260 in total on fractures every year.⁶ The cost to the patients is considerable. After sustaining a fracture of the hip approximately one-third of patients die within the first year,^{7,8} more than 50% are incapacitated and cannot walk unaided

or climb stairs,^{1,9} and 20% require long-term residential care.⁶

We review current practice in reaching a diagnosis and determining the aetiology of the condition, the options for treatment and strategies for prevention which are already in use and others which may be employed in the future.

Taking an appropriate history. Orthopaedic surgeons have only recently been introduced to the essentials of taking a history in osteoporosis. This should focus on the principal factors known to be responsible for the development of the condition so that intervention can be targeted at the main causes. Most individuals with osteoporosis are women, and thus the bulk of the investigations and regimes of treatment is aimed at dealing with the effects of the menopause and oestrogen withdrawal in particular. Up to 30% of all fractures of the hip occur in males,¹⁰ however, and the European Vertebral Osteoporosis Study has reported that the overall prevalence of vertebral deformity is similar for men and women between 55 and 74 years of age.¹¹

Risk factors for men with osteoporosis. When treating men with insufficiency fractures, both general risk factors for osteoporosis and those specific to men should be borne in mind. These include: hypogonadism, thyroid dysfunction, a low body mass index ($<19 \text{ kg/m}^2$), smoking, high alcohol consumption, long-term corticosteroid therapy ($>7.5 \text{ mg}$ of prednisolone for $>\text{six months}$), physical inactivity and diseases which predispose to low bone mass and neuromuscular dysfunction. Up to 40% of men with severe osteoporosis, however, have no identifiable cause or risk factor to explain their bone loss.^{12,13} The peak bone mass is as important as the rate of bone loss. Race, genetic factors, diet and exercise all contribute to the peak bone mass, but the most obvious influence is hormonal and the timing of the onset of puberty.¹⁴

Risk factors for women with osteoporosis. The risk factors which are important when considering women, and strategies for their treatment, are those listed above for men together with specific ones including a maternal history of fractures after minor trauma, or a past history of fragility fractures, loss of height and thoracic kyphosis, an early menopause (<45 years of age) either natural or surgically induced, a late menarche, prolonged secondary amenorrhoea (>1 year) and early hysterectomy.

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Fig. 1a

Fig. 1b

Scanning electron micrographs of normal (left) and osteoporotic (right) bone.

Hip Fracture Rates in Nottingham (1971 to 2000)

Fig. 2

The rates of fracture of the hip in Nottingham between 1971 and 1998.

Neoplastic causes for osteopenic bone should always be borne in mind. Myeloma and metastases from other tumours are relatively common.

With such a large and diverse list of risk factors to recall when reviewing a patient with a simple insufficiency fracture in a busy clinic, it is easy to dismiss the underlying cause and simply 'treat the fracture'. We should ask, however, if it is the responsibility of the surgeon to diagnose and treat osteoporosis. In our view the orthopaedic surgeon should alert the patients to the possibility that their fracture is a result of osteoporosis, and then direct them to their general practitioner or a lead physician in the management of osteoporosis. It has been shown repeatedly that there is a significant correlation between a low bone mineral density (BMD) and an increased risk of fracture.^{15,16} The reverse correlation has also been demonstrated clinically; in one recent study in the UK, women under the age of 65 years who had sustained a Colles' fracture had a significantly lower BMD of the hip than their age-matched peers.¹⁷

The initial fracture as a risk factor for osteoporosis. Active intervention to treat osteoporosis after a first fracture in an effort to prevent subsequent fractures is not routine current practice. In a recent retrospective study of over

1000 postmenopausal women who had sustained a fracture of the distal radius only 24% underwent either diagnostic evaluation by the clinician or treatment for the condition.¹⁸ The rate of treatment also showed a significant inverse relationship with advancing age. Indeed, in the UK, it seems that only vertebral fractures are associated with an increase in the prescription of drugs for the secondary prevention of fractures, and this was seen in only 39% of the cases studied.¹⁹

The reason for such neglect of prevention is related to the availability of both time and resources. Intervention has also been hindered by the lack of an 'algorithmically-based' protocol for treating this disease. Most cases are in elderly postmenopausal women who may not have a previous history of a fragility fracture. Apart from their fracture they may be completely asymptomatic and unaware of any underlying paucity of BMD.

The diagnosis of osteoporosis

Plain radiographs, while important in the diagnosis and management of fractures, are of little use in quantifying and managing osteoporosis. The accepted investigation is dual energy x-ray absorptiometry (DXA), which the World Health Organisation (WHO) has used to provide a quantifiable definition of osteoporosis²⁰ (Table I). It is a relatively cheap, non-invasive, safe and fairly accessible means of diagnosing and monitoring the disease. The BMD readings obtained are either compared with the young adult reference range (T-scores) or with those of an age-matched

Table I. Interpretation of DXA scores

Normal	BMD up to ± 1 SD of the mean of the young adult reference range
Osteopenia	BMD between 1 and 2.5 SD below the mean of the young adult reference range
Osteoporosis	BMD greater than 2.5 SD below the mean of the young adult reference range
Severe osteoporosis	BMD greater than 2.5 SD below the mean of the young adult reference range in the presence of one or more insufficiency fractures

Fig. 3a

Fig. 3b

Fig. 3c

Anteroposterior DXA scan (a) of the lumbar spine with 'above normal' BMD (b) compared with an obviously 'abnormal' lateral radiograph (osteopenia with wedging, etc) (c).

control group (Z-scores). Since the T-score is a comparison with the 'best ever' BMD it represents an absolute risk of fracture. The Z-score is a comparison within different age ranges and represents a relative risk of fracture.

While trabecular bone occupies only approximately 20% of the total skeletal mass, about 80% of all resorption and remodelling takes place there. Remodelling is a 'surface' phenomenon and trabecular bone has a much greater surface area than cortical bone.²¹ The most common sites examined therefore are the lumbar spine, the hip and the distal radius because of the relatively high ratio of trabecular to cortical bone present in these areas. The distal radius shows much anatomical variation in the proportion of cortical to trabecular bone. Hence the accuracy and reproducibility of the readings, even within a given individual, are worse than those for the hip and spine, and it is being used less and less in clinical trials. Portable peripheral DXA scanners, however, may prove to be useful in the community or in places where access to a full-scale DXA machine is not available.

Many authors have shown that the compressive strength of trabecular bone is proportional to its BMD.¹⁵ This correlates with a number of prospective studies which demonstrate the inverse relationship between bone mass and risk of fracture. It has been reported that for every

standard deviation of decrease in the BMD at the hip, the risk of fracture increases by a factor of 2.6.¹⁶ While DXA provides a quantitative measure of bone mass, it should never be used initially in isolation, since it cannot always reveal the gross morphological deformities seen on plain radiographs. This is a particular problem in the presence of osteoarthritis since osteophytes can result in the recording of spuriously high readings (Fig. 3).

Ultrasound and quantitative CT. Other radiological investigations used in the diagnosis of osteoporosis include quantitative ultrasound (QUS) and quantitative CT (QCT). Water-based calcaneal QUS is cheap and portable. Its use in the diagnosis and monitoring of osteoporosis is not yet universally agreed. The Guidelines from the Royal College of Physicians² support the use of QUS "for the assessment of the risk of fracture in institutionalised elderly women", but suggest that its role in monitoring the rates of change in BMD during the course of clinical treatment, or in the progression of the disease itself, requires further investigation. This is because of the large variability of individual ultrasound measurements in single patients.

QCT has been adapted for the spine and for the periphery, but with the advent of spiral CT, it may also be applied to measurements of proximal femoral BMD. The principal advantage of QCT is that the value received is a true

Table II. Biochemical markers used in assessing bone turnover

Bone formation (osteoblast products)
Alkaline phosphatase (serum)
Total activity
Bone-specific enzyme
Osteocalcin (serum)
Bone resorption (osteoclast products)
Propeptides of type-I collagen (serum)
C-propeptide
N-propeptide
Tartrate-resistant acid phosphatase (serum)
Hydroxyproline (urine)
Hydroxylysine glycosides (urine)
Collagen cross-links (urine and serum)
Total pyridinolines
Free pyridinolines
Cross linked N- and C-telopeptides

volumetric figure for BMD and not a two-dimensional, area-corrected result, as is obtained with DXA. It is expensive, however, and the patient is exposed to a higher level of radiation.

There are a number of biochemical markers of bone turnover available in most hospital laboratories. They can be broadly divided into those which assess the formation of bone and those which indicate resorption (Table II). Their use, however, has traditionally remained in the domain of the specialist in metabolic bone disease. These tests should not be ordered routinely by the orthopaedic surgeon. They are, as yet, not sufficiently discriminatory to be used in isolation as diagnostic tools, but can be employed as adjuncts to the investigations already discussed and to monitor trends in treatment. The Royal College of Physicians² suggests that a combined approach to the diagnosis of osteoporosis incorporating clinical risk factors, measurements of bone mass and indices of bone turnover would give the best assessment of the risk of fracture. Currently, however, there is not enough conclusive evidence for an optimum combination of these tests to be defined in an algorithm for predicting such fractures. Until this is available, the use of these biochemical markers of bone turnover will probably not influence strategies of orthopaedic management.

The aim of the clinician in diagnostic assessment should be to try to establish the aetiology, eradicate differential causes, assess severity and thus determine a plan of treatment with monitoring of the baseline tests. As a minimum, a full blood count, measurement of the ESR and levels of calcium, phosphate and alkaline phosphatase, and liver function tests should be performed. It should be remembered that after an acute fracture the level of serum alkaline phosphatase will rise to pathological levels by five days after the injury. Serum taken less than 48 hours after the fracture has occurred will give a good indication of the level of alkaline phosphatase before the injury. The gender of the patient, the age of presentation and any other salient points in the history will determine any specialist investiga-

tions such as measurement of the levels of testosterone, parathyroid hormone and 25-hydroxyvitamin D, thyroid function tests and bone turnover.

The prevention of osteoporotic fractures

This should be targeted at those with multiple risk factors for developing the disease.

Mild and moderate impact exercise. Encouragement of an active lifestyle with mild to moderate impact type exercise will undoubtedly contribute to protecting the bone stock. There are many epidemiological studies which support this hypothesis, with sufficient evidence to suggest that all types of insufficiency fracture, including those around the hip, can be reduced.^{22,23} This may be due to greater neuromuscular control and appears to be enhanced by a high intake of calcium. Regular impact loading of bone probably explains in part why larger people sustain fewer fractures after minor trauma, but other factors include the conversion of oestrone within adipose tissue in postmenopausal women.

Hip protectors. A randomised study of residents in a nursing home has shown that wearing of such a protector gives a significant reduction of hip fractures.²⁴ Compliance with wearing such a garment may be a problem in the more 'appearance-conscious' individual since eight of the patients in the study group sustained their fracture while not wearing the protector. Further work has shown that the effect of hip protectors in a fitter osteopenic elderly population is minimal (Lauritzen, personal communication).

Drug prophylaxis. Of the pharmacological preparations available for the prevention of osteoporosis we will briefly review the following: hormone replacement therapy (HRT), tibolone and selective oestrogen receptor modulators (SERMS). Other agents will be considered in the section dealing with treating established osteoporosis.

HRT still remains the treatment of choice in perimenopausal and early postmenopausal women. Apart from its effect on maintaining bone mass, it also alleviates the symptoms of the menopause such as vasomotor flushing and sweating. It also has a significant cardioprotective effect. While there are no specific randomised, controlled trials to support its use in the primary prevention of coronary heart disease, there is a large body of evidence to suggest that postmenopausal women taking HRT have a decrease in the incidence of coronary heart disease of up to 50% compared with those who are not receiving it. There is currently no such consensus of opinion when examining the relationship between HRT and strokes.

The less desirable effects of HRT include the return of menstrual bleeding and the associated risk of endometrial and breast cancer. The risks of endometrial cancer are virtually abolished if women with an intact uterus take cyclical oestrogen preparations.²⁵ Concern over the use of HRT and the risk of breast cancer is still a problem in most women about to commence treatment. The Collaborative

Group on Hormonal Factors in Breast Cancer²⁶ (CGHFBC) examined the data from 51 observational studies (>160 000 women worldwide). They concluded that those who had never used HRT could expect a cumulative incidence of breast cancer of about 45/1000 women. There was no increase in the incidence of breast cancer in those who used HRT for less than five years. After five years the risk increased. In women who used HRT from the age of 50 years the incidence of breast cancer was 47/1000 after five years, 51/1000 after 10 years and 57/1000 after 15 years. There was no excess risk detectable after five years of cessation of use. There are some data to suggest that although there is an increase in incidence, the mortality due to breast cancer may decrease. This may be due to women having greater self-awareness and surveillance while taking the treatment, and thus presenting earlier when breast lumps are found.

Recent information has shown an increase in the incidence of thromboembolism, and in particular idiopathic pulmonary embolism, in conjunction with the use of HRT.²⁷ Information concerning the route of administration is inconclusive but non-oral (patch or injection) are more deleterious than oral preparations.

Rapid bone loss occurs for several years after the menopause in women. By the age of 65 years, approximately 25% of the peak bone mass has been lost. This rate is somewhat attenuated in later years and between the ages of 65 and 75 years only a further 4% is lost.²⁸ HRT almost completely halts the rapid rate of bone loss seen in the immediate postmenopausal period. The beneficial effects of HRT, however, begin to reverse once the treatment has been stopped and have disappeared almost completely by several years after discontinuation of its use. The evidence concerning this is contradictory^{29,30} and the exact time frame over which this occurs is probably multifactorial and dependent on the individual. This remains a contentious issue. We know that 40% of women who take HRT cease to do so within the first year of treatment. If a woman continued treatment with HRT for ten years after the onset of the menopause she would, on average, have the equivalent bone stock of a woman of 65 years when she was 75 years of age. It is, however, from this age of her life onwards that she is at most risk of sustaining a hip fracture, and without further treatment her bone stock will diminish to pretreatment levels. This suggests that only long-term HRT will have a major effect on the prevention of osteoporotic fractures.

There are numerous studies showing the efficacy of HRT in maintaining or increasing the BMD at all sites,³¹⁻³³ including the neck of the femur. Some randomised, placebo-controlled, double-blind and prospective studies have shown a reduction in vertebral fractures,³¹ but as yet there is no equivalent information which shows a similar effect on the rates of fractures about the hip. There is epidemiological evidence to support this, but the non-skeletal benefits of HRT are such that it is difficult ethically to arrange proper randomised trials.

Tibolone is a synthetic analogue of the gonadal steroids and thus has oestrogenic, progestogenic and androgenic properties. It has similar vasomotor capabilities to HRT but does not cause withdrawal bleeding because of a lack of resultant endometrial hyperplasia. An increase in the BMD of the spine after two years of treatment has been shown³⁴ and there are some non-randomised data which suggest an increase at all sites.³⁵ It is only recommended for those women who have been over the menopause for at least one year. The cardioprotective effects are not yet fully established, but it does have some undesirable androgenic effects.

SERMS include raloxifene and tamoxifen (a clomiphene analogue) among others. The principal use of tamoxifen is in the adjuvant treatment of breast cancer but they all have oestrogenic properties in their own right. While tamoxifen does have some bone-preserving properties, it is currently not licensed for the treatment or the prevention of osteoporosis. Raloxifene has been shown to prevent bone loss and decrease the incidence of vertebral fractures in postmenopausal women^{36,37} and has been granted a licence for use in the prevention of such fractures. There are, as yet, no comparable reports which show a reduction in fractures of the neck of the femur.

Local arrangements for prophylaxis against osteoporosis. Within each District Health Authority in England and Wales a lead clinician has been identified who is responsible for developing the local protocol for the management of osteoporosis. The Nottingham flow-chart for osteoporosis is shown in Figure 4.

Treatment of established osteoporosis

The use of HRT has been reviewed in the previous section. There is some evidence to support its use in established osteoporosis, but while it appears to arrest declining BMD in elderly women there is some indication that it reduces the rate of fractures of the hip. It may decrease the incidence of vertebral fractures,³¹ but elderly, late postmenopausal women may not take it because they do not like the return of menstrual bleeding.

Calcium supplements used solely³⁸ or in conjunction with vitamin D³⁹⁻⁴¹ have been shown to prevent bone loss and also to reduce the incidence of fractures of the vertebrae and hip, especially in the elderly. The reduction in non-vertebral fractures was reported to be more than 50% in those over 65 years of age living in the community who were suspected of being depleted in these nutrients.⁴¹ It is probably most effective in the institutionalised who may have an inadequate diet and lack exposure to sunlight. The recommended daily intake is 1000 to 1500 mg for elemental calcium and 800 IU for vitamin D. In terms of compliance, vitamin D can be administered as an injection every six months. It is, however, most often taken as a preparation with calcium on a daily basis.

Bisphosphonates inhibit osteoclastic-driven bone resorp-

GUIDELINES ON THE MANAGEMENT OF ESTABLISHED OSTEOPOROSIS

The aim is to target treatment at those patients who are at the greatest risk of future osteoporotic fractures i.e. those who already have both osteoporosis and low trauma fracture.

MANAGEMENT IN PRIMARY CARE

Fig. 4

The Nottingham protocol for the management of osteoporosis (with acknowledgement to Professor D. Hosking, City Hospital, Nottingham, UK).

tion and reduce bone turnover. Several are available for the treatment and prevention of osteoporosis including etidronate, alendronate and risedronate. They generally have a very low bioavailability (<5%) and their optimal absorption occurs when taken after fasting. The length of time required to fast varies with each preparation; etidronate must be taken in the middle of a four-hour fast, while risedronate and alendronate can be taken first thing in the morning with water, at least 30 minutes before having food and drink.

Etidronate is normally given as a cyclical preparation over 90 days with a calcium supplement on 76 of the days

of treatment. It has been shown to reduce the rate of vertebral fracture in two randomised, controlled trials.^{42,43}

In the study by Storm et al⁴² only 66 patients were recruited and the results are therefore not comparable with the larger numbers mentioned later. These data only reach significance in the second and third years of the trial. Watts et al⁴³ recruited 429 postmenopausal women and demonstrated a ten-fold decrease in the incidence of vertebral fractures compared with most other series; the power of their study was probably inadequate. There are no significant data showing a reduction in the rates of fracture of the hip with cyclical etidronate, although there is retrospective epidem-

iological information collected from general practitioners to suggest that this may be the case.⁴⁴

Risedronate has been shown to give a significant reduction in new vertebral fractures in two large randomised, controlled trials.^{45,46} Significance of the data was reached within the first year. Calcium and vitamin D were supplemented in both studies as required. A reduction in fractures of the hip was demonstrated but did not reach statistical significance.

Alendronate has been studied extensively, but perhaps the most comprehensive trial which examined its efficacy in over 2000 osteoporotic women was the Fracture Intervention Trial (FIT).⁴⁷ This reported a reduction of 50% in the risk of sustaining a fracture of the hip, wrist or vertebra in women aged between 55 and 81 years with low BMD and at least one previous vertebral fracture. Follow-up was for three years and all subjects received calcium supplementation. Significance was reached within the first year of treatment. As a follow-up to this study, a group of women without a previous fracture, but who were still osteoporotic, was also analysed.⁴⁸ They showed a similar increase in BMD and a reduction in the rate of vertebral fracture after treatment. Little protective effect was found in those who had started the trial with a higher BMD.

Bone mass appears to be maintained for at least a year after cessation of treatment,⁴⁹ which suggests the possibility of long-term cyclical therapy which would reduce cost and side-effects while preserving bone mass.

Other treatments for established osteoporosis include calcitonin, calcitriol, fluorides and the anabolic steroids. Although they may have their place in the treatment of this disease, they should be left to specialists in bone metabolism.

Summary

Osteoporosis poses a significant orthopaedic problem of epidemic proportions. Clear guidelines for the management of osteoporosis presenting early or late are still being debated. Several recommendations, however, are now generally accepted.

Measurements of BMD should be taken if the diagnosis is in doubt or as an adjunct to encourage patient compliance with treatment. Those with multiple risk factors and who are under the age of 65 years would benefit from a scan. Those with previous fractures and no obvious risk factors should also be sent for DXA assessment. The elderly with fractures and multiple risk factors do not need scanning and can normally be started on treatment. Mass population screening is not cost-effective.

Prevention strategies should be targeted at high-risk patients and not offered to everyone. In the perimenopausal woman HRT is the first line of treatment and prevention, along with changes in lifestyle. Tibolone may be an option for those who find cyclical bleeding unacceptable.

In the elderly, institutionalised patient, calcium and vita-

min-D supplements should be considered to replace depleted levels, particularly for secondary prevention.

Postmenopausal women with multiple risk factors and at least one insufficiency fracture should be treated. The most likely pharmacological agent will be a bisphosphonate with supplemental calcium if indicated.

Each hospital should have a recognised link person through whom referrals can be channelled, either a clinical nurse specialist or physician. A protocol for treatment should be agreed locally and publicised among the primary health-care groups. The first step of identification of high-risk patients is most often in fracture clinics. Standardised letters attached to the clinic note to general practitioners are an easy way of 'getting these patients into the system'.

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