

Osteoporosis: Investigating a Silent Thief

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Abstract

Osteoporosis is a major cause of morbidity, long term disability and mortality, particularly among elderly postmenopausal women. The high prevalence of osteoporosis calls for effective screening programmes, particularly when due attention is given to the large health expenditure the disease incurs annually. The events involved in bone turnover and remodelling are complex and the derangements of this system, which lead to osteoporosis, are subtle. However, effective treatments for osteoporosis do exist, in the form of lifestyle modification and pharmacotherapy. Since bone deterioration in osteoporosis is progressive and self-perpetuating, these therapies become less efficacious as the disease progresses. The improved therapeutic outcome associated with early diagnosis further highlights the need for an osteoporosis screening programme. Unfortunately, several limitations currently hamper the establishment of generalised osteoporosis screening. The pathogenesis of osteoporosis remains incompletely understood. In the absence of a disease model which accounts for the genetic factors governing disease progression, the predictive accuracy of screening techniques for osteoporosis is low. Assessment of osteoporosis has hitherto been based on the measurement of bone mineral density. While this parameter is useful for diagnostic and monitoring purposes, its use in screening has been limited. Thus, osteoporosis screening programmes are not feasible until such time as: (i) a meaningful screening measurement can be devised and (ii) a more complete understanding of the disease is achieved.

INTRODUCTION

According to the International Osteoporosis Foundation, there is an osteoporotic fracture every 30 seconds in the European Union. One in three women and one in 12 men will develop osteoporosis in their lifetime. More women die following hip fractures than from cancers of the ovary, cervix and uterus combined.¹ Two hundred thousand osteoporotic fractures occur annually in the United Kingdom (UK), at a cost to the National Health Service (NHS) of £940 million (1.36 billion). The sheer magnitude of the problem, both in terms of prevalence and economic burden, highlights the need for more effective screening programmes for osteoporosis. This need is further underlined by the estimate that the number of osteoporotic fractures will double in the next 50 years due to an ageing population, if changes are not made in present practice.² The estimated worldwide annual cost of hip fracture alone will reach 132 billion by 2050.³

Definition

The WHO defines osteoporosis as a bone mineral density (BMD) of 2.5 or more standard deviations below the mean value for the general population. Osteoporosis can also be defined on a clinical basis as the occurrence of a minimal trauma fracture in an adult.³ It is characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and an increase in fracture risk. The WHO has

compared osteoporosis with hypercholesterolaemia and hypertension, both of which are asymptomatic conditions until an important tissue damaging event such as myocardial infarction or stroke occurs. In the case of osteoporosis, the first manifestation is the occurrence of a pathological fracture.

Epidemiology

Over 80 percent of hip fractures occur in women and more than 90 percent of these occur over the age of 50 years.² According to the WHO, most osteoporotic fractures occur in older women, resulting from a natural decline in bone density after menopause. Women are three times more likely to suffer such a fracture than men (lifetime risk of 40 percent for women compared with 13 percent for men).³ Certain other population subsets are affected by the disease, but represent a small fraction of the overall disease incidence. The relevant groups include elderly males or males suffering from hypogonadism; premenopausal females suffering from conditions such as anorexia nervosa or starvation⁴; ballet dancers and other participants in energetic sports⁵ and endurance sports⁶⁻⁸; those suffering primary or secondary amenorrhoea^{4,9}; children suffering from congenital defects in osteogenesis or bone mineralization.¹⁰

CAUSES OF OSTEOPOROSIS

Risk factors for the development of osteoporosis can be discussed in terms of: (i) modifiable factors, including cigarette smoking, low body mass (less than 58 kg), oestrogen deficiency, low calcium intake, and inadequate physical activity; or, (ii) non-modifiable factors such as previous history of fracture as an adult, family history of fracture, old age, female gender and genetic factors.¹²

Osteoporosis can be categorised as either primary or secondary, according to aetiology. Primary or idiopathic osteoporosis is the more common form, referring to the occurrence of osteoporosis in individuals where no definable medical cause can be found. Primary disease can be further divided into type I (oestrogen deficiency) or type II (senile). Secondary osteoporosis occurs as a consequence of an underlying condition that predisposes to bone loss. The secondary causes of osteoporosis account for 30 to 60 percent of cases in males and more than 50 percent of cases in premenopausal women. In postmenopausal women, the prevalence of secondary causes is much lower.¹²

The secondary causes of osteoporosis are numerous; the major causes are given in Table 1.

Causes	Example
Endocrine disorders	Gonadal insufficiency, cushingoid syndromes, hyperparathyroidism, hyperthyroidism, acromegaly.
Gastrointestinal disease	Any GI disease compromising Ca ²⁺ absorption
Marrow-related disorders	The majority of medullary disorders affect BMD, through imbalance in the distribution of pro-resorptive cytokines. Examples of conditions in which osteoporosis is a notable complication include multiple myeloma, lymphoma, leukaemia and thalassaemia.
Genetic disorders	Cystic fibrosis, osteogenesis imperfecta, various connective tissue disorders
Drug-induced	Glucocorticoids (>5mg/day prednisolone or equivalent, for >3 months), anticonvulsants, anticoagulants, GnRH agonists, lithium, thyroid hormone therapy
Miscellaneous causes	Alcohol abuse, ankylosing spondylitis, rheumatoid arthritis, COPD

Table 1. Secondary Causes of Osteoporosis¹²

CLINICAL MANIFESTATIONS

Osteoporosis is a silent disease associated with a characteristic set of fractures which, in order of occurrence, are:

(i) Vertebral fracture: Vertebral compression fractures affect approximately 25 percent of all postmenopausal women in the United States.¹⁴

The prevalence of vertebral deformities caused by osteoporosis is estimated at approximately 11 per 100 women aged 50 to 59 years and 54 per 100 in those 80 years of age and older.¹⁵ However, only one in four vertebral fractures are clinically diagnosed and the reported fracture incidence is lower than expected.¹⁶ Compression fractures vary in severity from mild wedges to complete compression, usually affecting the T8 to L3 vertebrae. Loss of height and kyphosis may be the only manifestations of vertebral fracture (accompanied in some cases by restrictive lung disease). At the other extreme, the condition may give rise to acute and debilitating pain.¹²

(ii) Hip fracture: In the UK, 60,000 osteoporotic hip fractures occur annually, accounting for more than 20 percent of orthopaedic bed occupancy.² Hip fractures are by far the most serious outcome of osteoporosis, associated with a high degree of morbidity and mortality, particularly in the elderly. Thirty-three percent of individuals hospitalised due to hip fracture die within one year, while 50 percent suffer significant disability. Men have less than 50 percent of the female risk for the development of hip fracture, but twice the mortality rate. Half of all osteoporotic hip fractures are intertrochanteric, the other half being fractures of the femoral neck.¹² Any intracapsular fracture may compromise blood supply to the femoral head, resulting in avascular necrosis, which significantly worsens prognosis.

(iii) Colles' fracture of the distal radius: 50,000 such fractures occur in the UK annually², typically resulting from falls in which the outstretched arm is used to prevent impact. The distal fragment of the radius is displaced dorsally and proximally, overriding the proximal fragment to give rise to the characteristic "dinner fork deformity". These tend to be less debilitating than other pathological fractures, causing short-term disability for approximately four to eight weeks. Patients with osteoporotic wrist fractures, statistically, are seen to suffer subsequent fractures, especially of the hip.¹²

(iv) Rib fracture: Apart from hip and wrist fractures and vertebral crush injury, 40,000 "other" osteoporotic fractures occur annually in the UK². Rib fractures account for the majority of these. In contrast to the other sites of osteoporotic fracture, ribs comprise a higher proportion of cortical bone. The vertebra and wrist are almost solely cancellous, while the hip is intermediate in terms of cancellous/cortical composition.¹¹

DIAGNOSIS AND MONITORING

A BMD value 2.5 standard deviations below the population mean is diagnostic of osteoporosis. Various techniques are available to measure BMD including single photon/x-ray absorptiometry, quantitative computed tomography and ultrasound. The most important technique currently used is dual energy x-ray absorptiometry (DEXA), considered to be the gold standard for measurement of BMD. Its purpose is threefold: (i) to diagnose osteoporosis, (ii) to monitor disease progression and (iii) to assess fracture risk. DEXA expresses BMD measurements in terms of normalised ratios, termed scores (Figure 2). The T-score compares the patient's BMD against the mean peak BMD, or the average value found in young healthy adults. The Z-score is an alternative measure and compares the patient's BMD with the average BMD for a gender and age-matched individual. The T-score is the more important measure, as fracture risk is related to an absolute BMD value. Though generally less relevant, Z-score becomes the more important measure at extremes of age, such as in young children or the very elderly.¹¹

Clinical investigation of suspected osteoporosis should be sufficiently broad as to rule out secondary causes. Thus, standard tests such as a full blood count, erythrocyte sedimentation rate, liver function tests and thyroid function tests should be carried out. Serum calcium, phosphate and alkaline phosphatase levels should be established to exclude osteomalacia or primary hyperparathyroidism. Serum and urine electrophoresis should be carried out to exclude multiple myeloma. Gonadal status should be assessed by assays for follicle stimulating hormone, luteinising hormone, testosterone,

oestradiol and progesterone (as appropriate for gender). The presence of hyperprolactinaemia or cushingoid disease should be assessed by measurement of prolactin and cortisol levels respectively. If metastatic bone disease is suspected, prostate specific antigen should be checked in males and a bone scan may be required. Biochemical markers of bone resorption include acid phosphatase, tartrate resistant acid phosphatase, hydroxyproline, hydroxylysine, pyridoxine, deoxypyridinoline residues, N-terminal telopeptides in urine and C-terminal telopeptides. The biochemical markers of bone formation include alkaline phosphatase, osteocalcin and C-terminal propeptides of type I procollagen. Biochemical markers should be measured before treatment, as well as three to six months after treatment is initiated.¹⁷

PREVENTION

Prevention of osteoporosis starts at an early age; diet, vitamin D and calcium intake, weight bearing exercise and menstrual status are important determinants of peak bone mass, which in turn impacts greatly on the subsequent risk of osteoporosis. In premenopausal women, a regular menstrual cycle providing normal levels of oestrogen and progesterone is essential. Irregular menstruation must be investigated.^{17,18} The combination of exercise, vitamin D and hormone replacement therapy (HRT), where indicated, is the optimum treatment to prevent bone loss. In postmenopausal women, a combination of exercise, calcium, vitamin D and antiresorptive therapy, should be used where appropriate. Antiresorptive therapies include selective oestrogen receptor modulators (SERMs), bisphosphonates, pulsed parathyroid hormone, and HRT.

Prevention of falls becomes an important consideration in the case of diagnosed osteoporosis. Muscle strength and coordination must be improved and eyesight deficit should be corrected. If the patient is underweight, hip protectors may be indicated. Sedating medications, including alcohol, should be avoided. The home environment should be modified where appropriate, to reduce the likelihood of falls.

TREATMENT OF OSTEOPOROSIS

General measures in the treatment of diagnosed osteoporosis include calcium and vitamin D

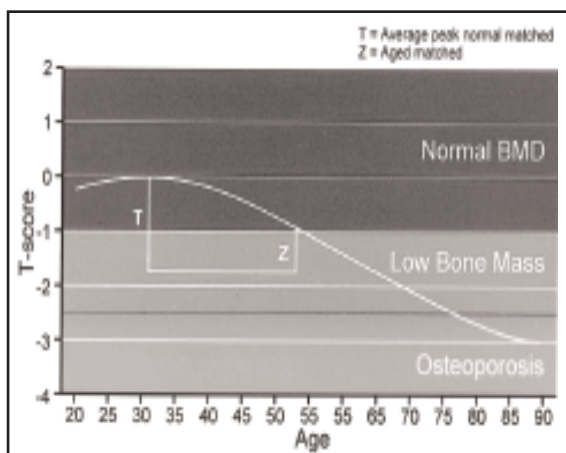


Figure 2. DEXA Assessment of BMD.

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supplementation (calcium: 1000 mg/day if less than 60 years, 1500 mg/day above 60 years; vitamin D: 800 IU/day).²⁴ Exercise, both weight bearing and muscle strengthening, is recommended as a means to increase bone density and to improve stability and self-sufficiency. Smoking cessation and limitation of alcohol intake are also encouraged.

Pharmacotherapy for osteoporosis is constantly evolving and considerable debate surrounds the choice of therapy to be considered as first-line. In order of clinical significance, the main therapies currently available include:

1. Bisphosphonates: A family of antiresorptive drugs which increase BMD and reduce the risk of vertebral, wrist and hip fractures. In recent years they have become the first-line therapy for osteoporosis. Alendronate and risedronate are the most popular agents used for this indication. Vitamin D supplementation is essential during bisphosphonate therapy.²⁴

2. Selective oestrogen receptor modulators (SERMs): A group of drugs that act as selective agonists of oestrogen receptors in bone and in the cardiovascular system, but antagonise similar receptors in breast and endometrial tissue. Thus, SERMs mimic the beneficial effects of oestrogen on bone, without the risk of endometrial and breast carcinomas associated with HRT. SERMs are, however, associated with an increased risk of thromboembolic events, similar to that associated with HRT. Raloxifene is the prototypical SERM. It is licensed for prophylaxis and treatment of vertebral fractures in postmenopausal women.²⁴

3. Pulsed parathyroid hormone (PTH) therapy : Whereas sustained elevation of PTH levels trigger bone resorption and thus have a negative effect on BMD, intermittent administration of PTH promotes net bone deposition, thus increasing BMD. Teriparatide is a recombinant preparation of PTH, which stimulates new bone formation when administered once daily.²⁴ It has been advised that it should be initiated by specialists experienced in osteoporosis therapy.²⁵

4. Calcitonin: If bisphosphonates are unsuitable, calcitriol or calcitonin may be considered. Calcitonin has both anti-resorptive and analgesic properties and may also be useful for pain relief for up to three months after a vertebral fracture if other analgesics are ineffective.²⁴

5. Hormone replacement therapy: HRT was, until recently, the mainstay of osteoporosis therapy. However, HRT is no longer recommended as a first-line therapy for osteoporosis and it is not recommended as a prophylactic treatment. The Women's Health Initiative Study revealed that HRT carried a significant risk of breast and endometrial malignancies, as well as thromboembolic events in postmenopausal women. Though it confirmed the beneficial antiresorptive effects associated with HRT with respect to hip and vertebral fracture (a risk reduction of 34 percent), the study also revealed that oestrogen plus progesterone replacement increased the occurrence of thromboembolic events and the long term risk of breast and gynaecological malignancies to an unacceptable degree.^{19-23, 31} In light of these findings, the Committee on Safety of Medicines in the UK has advised that HRT should not be used as first-line therapy for long term prevention of osteoporosis in women over 50 years and that it should only be considered where tolerance of other antiresorptive therapies is low.³² Other available therapies should first be explored and patients should be educated as to the potential risks associated with oestrogen and progesterone replacement in order to facilitate an informed choice.^{19, 23, 24, 26, 33}

Research into the mechanisms underlying osteoporosis is a continuing process. As knowledge of the pathogenesis improves, new therapeutic avenues are likely to become available. Current research is centred on the cellular mechanisms of BMD regulation and the heritable factors which influence osteoporotic risk. Possible new pharmacotherapies centre on signalling pathways known to modulate bone turnover. Examples currently under investigation include:

- Modification of the LDL-receptor-related protein 5/Wingless (Wnt) signalling pathway, involved in increased skeletal responsiveness to mechanical stimulation.^{27, 28}
- Modification of central bone mass regulation by leptin, mediated via the sympathetic nervous system, involving the alpha-melanocyte stimulating hormone/Agouti related peptide/melanocortin-4 receptor (a-MSH/AgRP/MC-4R) and the cocaine- and amphetamine-regulated transcript (CART) signalling pathways.^{27, 28}

- Modification of the Sclerostin-Bone Morphogenic Protein signalling pathway, involved in regulation of BMD, through the use of synthetic anti-SOST antibody.^{27, 28}

SCREENING

Despite the high prevalence of osteoporosis and the fact that the disease tends to be significantly advanced upon diagnosis, population-based screening for osteoporosis remains controversial.⁴⁰ There are a number of issues related to this, including the development of valid measures of osteoporotic risk and cost-effective screening technologies, defining the high risk population and diagnostic/intervention thresholds and understanding the burden of illness from the different osteoporotic fractures.

At present, DEXA scanning for BMD is the mainstay of osteoporosis assessment. However, there is no firm randomised controlled trial evidence to suggest that a screening approach based on DEXA would offer individuals accurate predictive information about osteoporotic fracture risk. While DEXA can yield high-accuracy measurements of BMD, the usefulness of this parameter as a predictive measure is debated. The variable rate of postmenopausal bone loss has been thought to correlate only moderately with BMD measurements at menopause. Thus, there is no BMD value which discriminates well between those who suffer fracture and those who do not.^{2,29}

It is hoped that the introduction of alternative technologies for osteoporosis screening may yield a more useful predictive measure than BMD alone. Prospective screening tools include:

- Ultrasound densitometry: Several methods have been developed which variously examine the velocity, attenuation or reflection of ultrasound. The potential advantages of ultrasound include cost, the absence of ionising radiation and the potential to assess structural organisation of bone in addition to BMD. Unfortunately, the accuracy and reproducibility of ultrasound BMD measurements have thus far proved unacceptably low.²
- Quantitative computed tomography (QCT) is another proposed alternative to DEXA. In QCT, a thin transverse slice through the body is imaged. This image can be quantified to give a measure of volumetric BMD and cancellous bone can be measured independently of

surrounding cortical bone and aortic calcification (which may distort readings with other techniques). The running costs and radiation dose of QCT are significantly higher than with absorptiometric techniques, however, calling into question the value of this method.²

Other risk factors which, by themselves or alongside BMD measurement, could predict osteoporotic risk are also being researched. Independent of BMD, these factors include a family history of fragility fracture, previous fragility fracture, biochemical markers of bone turnover and impaired neuromuscular functioning. These factors are all more prevalent in the elderly. Age remains the strongest risk factor.³⁸

The technological as well as cost limitations of generalised screening have given rise to attempts to devise a screening system that targets only those individuals most at risk, with a view to treatment. A recent population-based study in the United States has found that screening adults from the age of 65 years with hip DEXA scans is associated with a 36 percent reduction in hip fractures over six years, compared with medical care alone.⁴⁰ Cost-effectiveness studies indicate that a high relative risk must be present before therapeutic interventions are efficient.³⁰ Targeting only high risk patients would result in failure to identify the majority of future fracture sufferers. Although DEXA scanning could reduce the number of hip fractures, limiting the screening to adults over 65 years could miss as much as 50 percent of the total osteoporosis cases, as Richy *et al.* have found. They propose a two-step approach to osteoporosis screening, using validated pre-screening tools such as SCORE, ORAI, OST and OSIRIS risk index questionnaires with perimenopausal women before referral for DEXA scanning, as cost-effective approaches to significantly reduce the economic burden of osteoporosis screening.³⁰

The cost burden of osteoporosis, to individuals suffering from osteoporosis as well as to health care systems, draws attention to the need for better screening methods. Hip fractures generate the most health-care expenditure of all the osteoporotic fractures and are often the subject of economic scrutiny. Kanis *et al.* state, however, that cost-effectiveness varies with the age at which the treatment is given. In their study of risk and burden of vertebral fractures, they found that reported loss of utility in the first year after a vertebral fracture was the same as that of a hip

fracture (37 percent) when compared with an individual in perfect health. Vertebral fractures occur earlier in osteoporosis than hip fractures and can incur a lifetime disability nearly two-thirds of that resulting from a hip fracture (62 percent). The morbidity and associated cost of other osteoporotic fractures is a significant consideration in younger individuals suffering from osteoporosis and have been poorly researched.^{36, 39}

Intervention thresholds are another important dimension in screening: at what relative risk of osteoporotic fracture does it become cost-effective to initiate treatment? Kanis *et al.* argue that diagnostic thresholds cannot be used as intervention thresholds in osteoporosis. They state that intervention thresholds need to be based, wherever possible, on absolute risks of all osteoporotic fractures, not just hip fractures.³⁶ The construction of appropriate intervention thresholds in osteoporosis is complicated by the variety of fractures which can occur and the differing outcomes associated with each. Studies have shown that a 10-year fracture risk is the most appropriate measure for determining intervention thresholds, in the same way that 10-year risk of an ischaemic event is used to guide therapy in the setting of IHD.³⁴⁻³⁷

In order to devise an integrated intervention threshold for all fractures, it may be useful to consider fractures at different ages in terms of the negative impact on quality of life. The benefit of this system is that all fracture types become comparable and the intervention threshold is no longer fracture specific, but outcome specific. If the morbidity resulting from a given fracture is

assumed to be proportional to the cost this fracture generates, intervention thresholds can now be established on an economic basis. Predictably, however, when this new model is used to integrate data on all fractures, the intervention threshold at which treatment becomes cost-effective is lowered, particularly in younger individuals. Thus, such a system tends to artificially decrease the intervention threshold to the point that it may be misleading. It becomes necessary to treat at a lower level of risk as assessed by screening techniques, such that it could conceivably be more cost-effective to treat all those potentially at risk than to establish screening programs at all.^{36, 37}

CONCLUSION

Although the institution of a nationwide osteoporosis screening programme is not feasible at this time, the cited research demonstrates the need for better screening methods of populations at risk and gives examples of several cost-effective means to achieve it. An incomplete scientific understanding of the disease and varying definitions of diagnostic and intervention thresholds are at the root of the problem. The clinical usefulness of DEXA screening is debatable, as there is substantial inter-individual variability in the subsequent outcome and because the genetic and environmental risk factors which contribute to this variability are poorly defined. The focus in osteoporosis therapy continues to centre on treatment, rather than prevention. The establishment of cost-effective intervention thresholds based on fracture risk is an inexact, though developing science. Osteoporosis screening remains a work in progress.

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