

Osteoporosis-The Need for a Paradigm Shift

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Abstract

Osteoporosis is a potentially devastating illness and causes morbidity and mortality from fragility fractures at the wrist, spine and hip. Currently, the illness can be detected before the fractures occur using dual energy X-ray absorptiometry and many preventive and therapeutic options exist. Efforts should be directed at helping the population at large achieve a healthy peak bone mass and adopt lifestyle habits which benefit bone mass. For those at high risk of fractures or who have already suffered an osteoporotic fracture, many pharmacological agents have been shown to reduce the risk of subsequent fractures. Hormone replacement therapy and bisphosphonates have the best efficacy data at present but there are likely to be more options in the near future. Hence, there is a need for a paradigm shift in that osteoporosis should not be thought of as an illness that starts at the point of fracture. Instead, it should be actively assessed and treated before fractures occur.

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Introduction

Osteoporosis is becoming an increasing public health problem in most countries. Osteoporosis literally means “porous bones” and involves skeletal fragility leading to an increased risk of fracture. Early diagnosis is now possible using precise methods of bone density measurement and therapies exist which can reduce the risk of fractures. Hence, there is a need for a paradigm shift in that we should not think of osteoporosis only at the stage of the osteoporotic fracture.

In both men and women, bone mineral density (BMD) increases from early childhood to a maximum in late teenage years. This “peak bone density” appears to be determined by a combination of genetic, environmental and life style factors. With increasing age both men and women lose bone gradually (age-related bone loss) and in women there is usually a rapid phase of bone loss immediately after menopause. Whilst important principles of management include maximising peak bone mass in early adult years and prevention of postmenopausal bone loss by oestrogen therapy, interventions later in life with oestrogens, bisphosphonates, calcitriol and calcitonin can also substantially reduce fracture risk.

Epidemiology

In Caucasian women aged ≥ 50 years, a lifetime risk of a first atraumatic vertebral deformity/fracture was esti-

mated to be 32%.¹ Studies in males have suggested similar or higher vertebral deformity prevalence rates. The lifetime risk of a Colles’ fracture in women is estimated at 15% and in Caucasian men of the same age at 2.4%.¹ Hip fractures from a public health perspective are a major osteoporotic fracture and it is estimated that for a 50-year-old Caucasian woman the lifetime risk of an osteoporotic hip fracture is 16%.

Worldwide trends suggest hip fracture rates will double in the next 20 years and the problem will rapidly escalate particularly in Asia.² The number of hip fractures worldwide is expected to rise from 1.66 million in 1990 to 6.26 million by the year 2050. The population in Singapore is going to become more aged in the next twenty years and so osteoporosis will become an even more significant problem in future.

In Singapore, data are lacking with respect to spine and wrist fractures but the annual incidence of osteoporotic hip fractures is estimated to be approximately 30 per 100 000 or about 1000 cases every year.³ In a study of the outcome of 280 hip fractures in Singapore (unpublished data-Wong M K, Lo N N), the mortality after the first year was 26% in spite of the fact that 90% were fit for surgery. Of the survivors, 24% were wheelchair bound and 9% were bedridden.

The annual direct costs of treating hip fractures alone has been estimated at 614 million pounds in the United Kingdom and \$10 billion in the USA.² The costs of

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treating hip fractures in 1996 in Singapore is estimated to be S\$6 million (unpublished data-Wong M K, Lo N N) and given our ageing population, this will rise to S\$35 million in 2030.

Clinical Features

The cardinal result of osteoporosis is fracture. Fractures typically occur after minimal trauma, often in the course of daily living. Osteoporotic fractures can occur in almost any bone and the clinical features vary according to the site of fracture. Before fractures occur, osteoporosis is largely a silent disease.

Wrist and Hip Fractures

Fractures at the wrist and hip usually follow falls. The likelihood of falling is increased by poor vision, impaired coordination, abnormal gait, co-existing neurologic and rheumatic diseases and use of sedating drugs.⁴ About 30% of subjects aged ≥ 65 years fall once or more per year but only 3% will sustain a fracture. The site of fracture can be influenced by the direction of the fall. Falls forward are more likely to result in distal radius or Colles' fractures and falls backwards are more likely to result in hip fractures. Hip fractures require hospitalisation for surgical treatment and are associated with a mortality of about 20% in the first year. Ongoing disability or the requirement for institutional care is frequent after hip fractures.

Vertebral Fractures

Vertebral fractures are often defined by measurements of vertebral dimensions on lateral radiographs of the spine. Such criteria essentially measure vertebral deformity and it has been assumed that changes in vertebral shape represent fracture, but it is increasingly recognised that deformities may arise by mechanisms other than fracture (e.g. Scheuermann's disease) and that not all deformities are clinically significant events.⁵ Nonetheless, a history of height loss and serial measurement of height are useful clinical indicators of osteoporotic spine fractures. Symptomatic spinal fractures typically present with acute back pain after sudden bending, lifting or coughing but the patient may just develop progressive kyphosis. Most vertebral fractures occur in the middle, lower thoracic and upper lumbar spine, most commonly the twelfth thoracic and first lumbar vertebrae. Acute episodes of pain usually settle after 1 to 2 months. Severe back pain which persists for many weeks is uncommon and the diagnosis of osteoporotic vertebral fracture should be questioned when this occurs. Further or multiple fractures may occur at variable intervals ranging from months to years leading to continuous dull back pain in association with a progressive dorsal kyphosis, often described as a "dowager's hump".

Clinical assessment of individual patients with osteoporosis should involve a consideration of risk factors and secondary causes of osteoporosis. Risk factors for osteoporosis generally include an early menopause, late menarche, long-term use of oral corticosteroids, reduced lifetime dietary calcium intake, smoking, lack of physical exercise and thin body habitus. Obesity appears to be protective against osteoporosis, probably related to greater skeletal loading and increased endogenous estrogen production in adipose tissue in postmenopausal women. Immobilisation is associated with bone loss and physical activity is positively related to BMD but as noted above, excess exercise may be harmful, especially in young females who develop exercise-induced amenorrhoea. Disease states such as thyrotoxicosis, malabsorption and conditions requiring high dose chronic glucocorticoid therapy, anti-convulsants and heparin are also associated with osteoporosis. Although these factors may give some indication of the risk of developing osteoporosis, they cannot be used to reliably identify individuals with osteopenia.

Specific risk factors for hip fractures include a maternal family history of hip fracture, a history of previous fractures, tall stature at age 25, a late menarche, previous hyperthyroidism, use of benzodiazepines or anti-convulsants, greater caffeine use, inability to rise from a chair without using the upper limbs, poor depth perception, poor visual contrast sensitivity and low appendicular BMD.⁶

Differential Diagnosis

Clinical biochemistry may be helpful in the differential diagnosis of osteoporosis. For example, hyperparathyroidism, osteomalacia and renal osteodystrophy may mimic osteoporosis but often will have abnormal laboratory findings of serum calcium, phosphate, alkaline phosphatase or parathyroid hormone.

Neoplastic conditions may cause diffuse loss of bone mineral which in some, but not all cases, will be associated with hypercalcaemia. Multiple myeloma may produce demineralisation with or without compression fractures. Unlike metastatic malignancy, myeloma usually spares the neural arch. Posterior wedging of a vertebra should suggest the possibility of metastatic malignancy as should spinal cord compression, since osteoporotic fractures rarely cause neurologic manifestations.

Diagnosis of Osteoporosis

Osteopenia may be apparent radiologically but up to 30% of BMD may be lost by this time. The lack of sensitivity of radiological methods has given rise to more precise quantitative methods of diagnosis. The two most common methods for quantitation of BMD are dual energy X-ray absorptiometry (often called DXA)

and modified quantitative computed tomography (sometimes called QCT). Generally DXA scanning allows better precision with shorter scanning time and a lower radiation dose than QCT.

Using DXA, BMD (usually expressed as g/cm²) is generally reported at two sites, the lumbar spine and femoral neck, but can be measured regionally at any site and whole body scans can also be performed.

It must be remembered that normal values for BMD differ between QCT and DXA machines and also between different types of QCT and DXA machines. The risk of fracture relates primarily to comparison with young normal values, rather than age-matched subjects and for these reasons, BMD is often expressed as a 't-score' or number of standard deviations (SDs) from the mean of a young normal population.

The following diagnostic categories have recently been proposed by the WHO:

- Normal: values above 1 SD below the young adult mean
- Low bone density or osteopaenia: values between 1 to 2.5 SD below the young adult mean
- Osteoporosis: values > 2.5 SD from the mean of young normal values

Using these criteria, the term "severe osteoporosis" is suggested for the situation of a low BMD value in conjunction with atraumatic fracture(s) having already occurred.

Inter-racial differences in BMD have been described. Among Singaporean Chinese women, BMD at the spine was about 5% lower than American white female control subjects. Similarly the femoral neck density of the Singaporean Chinese women was 8% lower than the Americans.⁷

Ultrasound techniques have been studied for diagnosis of osteoporosis and currently should not be used alone to guide treatment decisions.⁸ A whole range of newer biochemical markers of bone metabolism have recently been developed including markers of bone formation (such as serum osteocalcin, bone specific alkaline phosphatase and procollagen type I propeptide) and bone resorption (such as urinary pyridinolines, N terminal telopeptides and tartrateresistant acid phosphatase). These may provide additional information about bone turnover and response to therapy, but at this time remain research tools rather than diagnostic tools.

Management of Osteoporosis

Prevention

Diet and Lifestyle

As discussed above, although the relationship between dietary calcium and osteoporosis has been controversial, it is generally accepted that there is a significant

effect of calcium intake over the longer term and the effect may be especially relevant to the growing skeleton and in postmenopausal women. An adequate dietary calcium intake in Western countries involves at least 800 mg premenopausally and 1200 mg calcium per day in postmenopausal women. Calcium intake among Asians is generally lower than in Western countries because of cultural biases. However, it is also conceivable that Asians require less calcium than Caucasians. Ho et al⁹ found that among Hongkong Chinese women aged 21 to 44 years, the mean daily calcium intake was 448 mg/day. Subjects with the lowest calcium intake had the lowest BMD measurements. The main food source for calcium was from vegetables rather than milk. A food consumption study in 1993 by the Ministry of Health in Singapore showed that the mean daily intake of calcium for women was 448 mg while that for men is 508 mg. About 53% of men and 29% of women had calcium intake levels above 500 mg a day. Another study involving 175 women aged 21 to 80 years showed that only 22% drank milk everyday.⁷ In a recent study, Leong¹⁰ found that among 21-year-old Singaporean Chinese females, there was a significant contribution of calcium intake to peak bone mass. The average daily intake in these subjects was 632 mg. The vitamin D receptor genotype was not important in this cohort.

Physical activity also has a beneficial effect on bone density. Specific optimal exercise regimens have not been identified, but a reasonable approach is to encourage daily weight-bearing exercise. However, excessive exercise may be harmful, especially in young females, by leading to oligo-amenorrhoea. Exercise may also have a specific role in prevention of falls in the elderly by improving muscle strength.

Hormone Replacement Therapy

Menopause is the major factor contributing to the increased incidence of osteoporosis in women. Rapid bone loss occurs for up to 15 years after menopause and can exceed 25% of peak bone mass. Studies have clearly shown that oestrogen replacement therapy can prevent postmenopausal bone loss and reduce fracture risk" and there is now considerable evidence for a beneficial effect of oestrogen replacement in reduction of cardiovascular risk. Alternative routes of administration such as transdermal oestrogen have been developed and may decrease adverse effects such as weight gain and blood pressure effects. The risk of endometrial cancer appears to be obviated by concurrent cyclical or continuous low dose progestins therapy, but whether oestrogen is associated with any increased risk of breast cancer remains controversial.¹²

Research is ongoing in assessing the efficacy of a new class of agents named SERM's (selective estrogen receptor modulators). These agents have the potential to produce

the beneficial long term effects of hormone replacement therapy without the side effects. Delmas et al¹³ showed that reloxifene used over 24 months was able to preserve bone density and improve lipid profiles in women within 2 to 8 years after menopause.

Treatment of Established Osteoporosis

Restoration of bone strength when BMD is already markedly reduced is more difficult but there have been some promising recent advances. Moreover, although bone loss appears to be very rapid in the first few years after menopause, there is increasing evidence that bone loss continues beyond the age of 65 years and can actually increase in the very old.¹⁴ Consequently, agents that prevent further bone loss may actually be most cost-effective in the very elderly because older subjects have the greatest risk of fracture.

The most widely used treatments for established osteoporosis are anti-resorptive and act primarily to prevent further bone loss with only modest increases in bone density generally observed. There is however a significant decrease in the risk of fractures with treatment.

Bisphosphonates

Oestrogens have been shown to be beneficial in this clinical setting but acceptance for HRT in these older patients is often low. Storm et al¹⁵ reported that giving etidronate orally for 2 weeks followed by a 13-week period of no treatment repeated 10 times was effective in treating postmenopausal osteoporosis and preventing vertebral fracture. Importantly histomorphometric data revealed no evidence of impaired mineralisation in the subjects receiving etidronate. Similar results were obtained by Harris et al.¹⁶ In a larger, multicentred, randomised, placebo-controlled trial, the effects of the new bisphosphonate alendronate in 994 postmenopausal women have been reported.¹⁷ Alendronate has about 1000 times greater potency in terms of inhibiting bone resorption than etidronate and therefore allows effective inhibition of bone resorption at doses that do not affect mineralisation even when used continuously. Alendronate 10 mg a day produced gains in BMD at all sites. In the Fracture Intervention Trial,¹⁸ fracture risk reduction of about 50% at the wrist, spine and hip was seen in those who have sustained at least one vertebral fracture. Another arm of this trial found that alendronate also reduced fracture risk in those who have not yet suffered a fracture. Several other new bisphosphonates, including tiludronate and residronate, are also currently undergoing clinical trials in many countries.

Vitamin D and Analogues

Vitamin D plays a pivotal role in the regulation of calcium metabolism and its metabolites have been used

as therapy for osteoporosis for many years with variable results. Exposure to the sun causes human skin to make vitamin D. The elderly are less exposed to sunlight and the skin is not as healthy. One can also get vitamin D from diet. The elderly may not eat very well and the gut may not function normally. The kidney converts vitamin D into active forms but the ageing kidney may not be as efficient in doing this.

A recent study in France reported that treatment with vitamin D 800 IU plus calcium could reduce the frequency of hip fractures in the elderly, but these subjects generally had subclinical osteomalacia.¹⁹ Lips et al²⁰ failed to show a significant benefit of vitamin D alone in elderly subjects when employing the lower dose of 400 IU of vitamin D.

Calcitriol (1,25-dihydroxyvitamin D₃) is classified as an anti-resorptive agent by virtue of its ability to enhance gastrointestinal absorption of calcium and so decrease parathyroid hormone driven bone resorption. In the study by Tilyard et al,²¹ 622 women with established postmenopausal osteoporosis (defined by the presence of one or more atraumatic vertebral fractures) were randomly allocated to receive either calcitriol 0.50 micrograms daily or calcium gluconate. No difference in fracture rates were seen in the first year but in the second and third year a three-fold reduction in new vertebral fractures was seen in the calcitriol treated group. Peripheral fractures were also significantly reduced in the calcitriol-treated group and adverse events were low with this daily dosage of calcitriol. Previous clinical studies of calcitriol in established osteoporosis have yielded conflicting data with regards to bone density trends but the sample sizes of these studies were too small to allow proper evaluation of its effect on the incidence of fractures. Calcitriol appears to have particular advantages as a preventative agent in corticosteroid osteoporosis.²²

Calcitonin

Calcitonin is a 32 amino acid polypeptide with a molecular weight of 3500 daltons. While the physiological role of calcitonin in bone and mineral homeostasis is not well defined, it is a powerful inhibitor of osteoclastic bone resorption. Clinical studies of the use of calcitonin in postmenopausal osteoporosis have been encouraging. However, most have been of a relatively short duration and involved small numbers of patients.

Overgaard et al²³ observed a mean increase in lumbar spine BMD of 3% in patients receiving 200 IU calcitonin daily compared with 1% in the placebo (calcium) group. A dose response pattern was evident. Surprisingly there was no significant difference between groups in the forearm, where bone loss was observed. Moreover the clinical significance of the fracture data is unclear since, although the rate of new vertebral fractures was reduced

in the calcitonin group, the number of new fractures in each group was small.

Sodium Fluoride

Sodium fluoride increases trabecular BMD and fluoride has been widely used for many years but relatively few studies have been fully placebo controlled and double blind. Controlled studies of patients with postmenopausal osteoporosis funded by the United States National Institutes of Health demonstrated large increases in lumbar spine BMD from 75 mg of fluoride daily given for 4 years, but no reduction in vertebral fracture rate and an increase in peripheral fracture rates. New slow release formulations offer promise, but at this stage fluoride cannot be widely recommended.²⁴

Anabolic Steroids

The production of androgens from the adrenal gland declines with age. Some workers have shown that dehydroepiandrosterone sulphate, a serum marker of adrenal androgen production is significantly lower in osteoporotic as compared to non-osteoporotic postmenopausal women. Furthermore women with syndromes of androgen excess have higher than expected trabecular BMD. All these data support a role for androgens in the maintenance of bone mass after menopause.

Anabolic steroids are derived from naturally occurring androgens and have been used for the treatment of established osteoporosis. While data from clinical studies are encouraging there is a relatively high incidence of virilisation at effective doses and bone loss may recur following cessation of treatment.

Conclusion

Significant advances in our ability to diagnose, prevent and treat bone loss are occurring and there is increasing evidence that treating osteoporosis even in the elderly can decrease fracture risk. Maximisation of peak bone mass in early adult years and prevention of age and menopause-related bone loss will delay or prevent the occurrence of osteoporosis and its associated morbidity and mortality. A variety of agents are now also available for the treatment of established osteoporosis. Hence, osteoporosis should not be thought of as a disease where intervention starts at the point of fracture. Many effective prevention and treatment strategies exist which can reduce the impact of this potentially devastating illness in the decades ahead.

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