Osteoporosis – Recent Advances In Diagnosis And Treatment

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Summary

Osteoporosis is a highly prevalent disorder in the older population. The approach in management is towards identification of high risk patients for preventive and therapeutic measures. The diagnosis of osteoporosis and assessment of fracture risk can be made readily by measurement of bone mass with bone densitometry. Quantitative ultrasonometry is becoming popular as an initial test to identify patients who require further investigation. Coupled with the assessment of risk factors for osteoporosis, the use of bone mineral density can achieve high sensitivity and specificity in identifying subjects with high fracture risk. The role of hormone replacement therapy, selective oestrogen receptor modulators and other anti-resorptive agents such as bisphosphonates, calcitonin and vitamin D in treatment of osteoporosis are discussed. (HK Pract 1999;21:3-10)

摘要

骨質疏鬆症是年老人口中的高發症，治療重點旨在確認高危患者，並提供預防與治療。利用骨質密度（BMD）測量儀，骨質疏鬆診斷與評估骨折危機便能很易作出結論。超聲波骨質測量用為指導高危患者作進一步檢驗亦大受使用。如配合評估臨床有骨折高危因素，結合 BMD 來測定骨折危機會有很高的特異性及敏感性。本文並對治療骨質疏鬆症的各類藥物，分別作出討論。

Introduction

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

In the past, we often described osteoporosis as a silent disease. It did not reveal itself until it resulted in a fracture. But today it can be reliably diagnosed through radiology before fractures occur.

Causes of bone loss

The major cause of bone loss in women is oestrogen withdrawal associated with menopause. After attainment of peak bone mass, the average annual rate of bone loss is 1-2% in postmenopausal women and 0.2-0.5% in men. The loss is greatest in the early years after menopause, when annual rates of loss may be up to 3-5%. An additional increase in bone loss may occur after the age of 70 years. Epidemiology studies revealed a number of risk factors associated with increased bone loss and fracture risk (**Table 1**) in postmenopausal women. According to the EPIDOS study, these clinical risk factors are very useful in identifying subjects with low bone mass.[1] Using a 19 point scoring

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system, a score of ≥ 4 had a sensitivity of 93% in identifying subjects with low bone mineral density (BMD) with a specificity of 61%.

The pathogenesis of osteoporosis in men is less well established. Most have secondary causes including androgen insufficiency.

Assessment of fracture risk using BMD

Many factors determine the likelihood of fracture, including various skeletal abnormalities and non-skeletal considerations, such as falls. However, bone mass is perhaps the most important factor and is certainly the factor that can be quantified with precision. Consequently, both the diagnosis of osteoporosis and the assessment of fracture risk centered around bone mass measurement.

For diagnostic purposes, the WHO study group on assessment of fracture risk has proposed a threshold of BMD based on the T-score. The T-score reflects standard deviation (SD) from a young healthy adult population. A T-score of above -1 is considered normal and a score of -1 to -2.5 denotes low bone mass (or osteopenia). A T-score of -2.5 or less denotes osteoporosis. Established osteoporosis is defined as a T-score of -2.5 or less, with at least one documented fragility fracture, usually of the wrist, spine or hip.

BMD thresholds for osteoporosis in men have not been well studied but a similar absolute value to that used in women may be applicable. A normal BMD does not guarantee a fracture will not occur, only that the risk is lower. Similarly, BMD in the osteoporotic range indicates that fractures are likely, but not inevitable.

The risk of fracture approximately doubles for each 1 SD

decrease in BMD. Thus, the risk is increased more than four-fold in individuals with osteoporosis. It is doubled again in patients who have already had a fragility fracture. At the age of 50 years, the average life-time risk of the usual osteoporotic fractures among white people is approximately 13% in men and 40% in women. For Chinese women in Hong Kong, the cumulative life-time risk of having osteoporotic fractures is 25%.[2]

Techniques used to measure bone mass

Bone densitometry

Bone mass is usually measured using single- or dual-energy absorptiometry. Single-energy absorptiometry (SXA) is used to measure bone mass at peripheral (appendicular) sites including the heel and wrist. Bone mass at axial sites such as the spine and hip (where fractures often occur) cannot be accurately measured with SXA, necessitating the use of dual-energy absorptiometry. Either photons (DPA) or X-rays (DXA) can be used. Frequently measured sites included the hip, spine and forearm.[4] In Hong Kong, DXA is more widely available than DPA. **Figure 1** and **Table 2** show a typical dual energy X-ray absorptiometry (DEXA) scan of the lumbar spine and its analysis, respectively.

Quantitative ultrasonometry

Quantitative Ultrasonometry (QUS) is becoming more popular

Table 1: Risk factors for osteoporosis

- age
- low body mass
- oestrogen deficiency
- maternal history of fragility fracture
- low calcium intake
- inactivity
- smoking
- caffeine
- alcohol
- gastric surgery
- medications (e.g. glucocorticoid, thyroxine, phenytoin)

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Figure 1: Dual energy X-ray absorptiometry (DEXA) scan of the lumbar spine in an osteoporotic patient
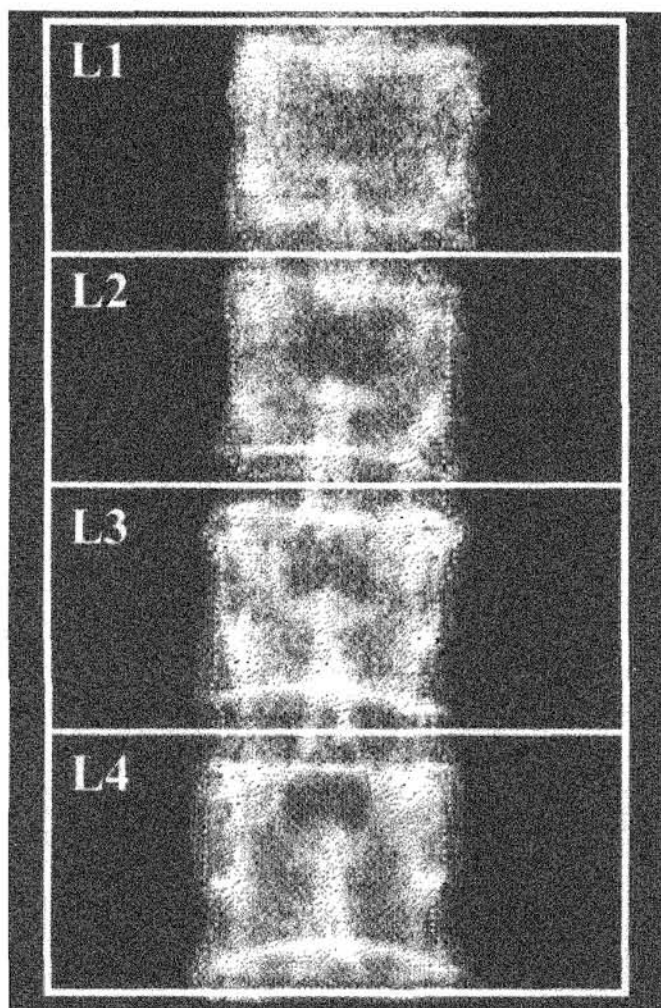

Table 2: DXA scan measurements at the lumbar spine of a 54-year-old woman with osteoporosis. The results are compared to both the premenopausal reference range (T-score) and an age-matched population (Z-score)

Region	BMD (g/cm²)	T-score		Z-score	
L1	0.573	-3.20	(62%)	-2.29	(70%)
L2	0.643	-2.72	(64%)	-2.14	(70%)
L3	0.749	-2.10	(73%)	-1.66	(77%)
L4	0.744	-3.38	(67%)	-2.28	(75%)
L1-L4	0.683	-3.31	(65%)	-2.25	(73%)

because it is cheap, radiation free, non-invasive and portable. QUS measures the broadband ultrasound attenuation and speed of sound as the ultrasound hits or passes through the bone. Some machines provide a stiffness index derived from these two parameters. Numerous studies have demonstrated that ultrasonometry of the heel, using both contact and water-based devices, has high predictive accuracy for fracture.[5] Prospective studies using water-based ultrasonometers show that heel ultrasound can predict the risk of fractures of both the spine and proximal femur in women over 70. The relative risk based on measurement of the stiffness index is comparable to axial BMD in these osteoporotic fractures.[6-7] There are no prospective studies demonstrating that the tibial device predicts hip fracture.

Other techniques

Other techniques for measuring bone mass include quantitative computed tomography and radiographic techniques. Quantitative computed tomography has limited clinical application due to the high dose of radiation exposure. Similarly, ordinary radiographs are inaccurate and insensitive and do not detect bone loss until 25 - 40% of the bone is already lost. However, this is how osteoporosis is often diagnosed.

Bone mass measurement in clinical practice

The most accurate prediction of fracture requires assessment of the

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site concerned. At the time of menopause, BMD measurements at the wrist, spine or hip are useful. But measurements at the hip are more valuable in the elderly, for whom hip fractures are the common major problem. The spine, however, may not be suitable in the elderly because of the presence of osteoarthritis. But response to treatment are often more marked at the spine than elsewhere and can be detected earlier than at the hip or wrist.

At present, QUS can help to identify patients who need further testing. Ultrasonometry of the os calcis provides independent information on risk of both spine and hip fracture, even though the correlation with BMD at these sites is only about 0.5 to 0.7.[8] It is believed that QUS provides information other than bone density, such as the stiffness and connectivity of the bone. One of the remaining questions is the extent to which ultrasonometry predicts fracture in the early post-menopausal years. The challenge in the next few years will be the appropriate use of ultrasonometry of the heel, especially its use in monitoring treatment efficacy. At present, the use of QUS is limited by the poor precision and accuracy of QUS when compared to DEXA.

Clinical approach towards patient identification

Mass screening of BMD is not justified as it is not cost-effective. The use of BMD alone to assess risk has high specificity but low sensitivity. The approach therefore is towards identification of high risk cases for therapeutic and preventive

treatment.[3] The patient's history and the results of physical and biochemical examination should be taken into account for decision for BMD measurements. Some of the indications for BMD measurement are shown in **Table 3**.

Treatment of osteoporosis

The objective of all measures to prevent and treat osteoporosis is the same – to achieve or maintain bone density at a level that the risk of fractures is low.

Hormone replacement therapy (HRT)

Oestrogen is the oldest and most common treatment for osteoporosis.

Recent reports have indicated that over a 3-year period, women who stayed on any HRT regimen – with or without a progestogen – had an average increase in bone density of 4% at the spine and 2% at the hip. Those taking placebo registered losses in bone density averaging 1.8% at the spine and 1.7% at the hip.[9] HRT also has a favourable effect on cholesterol and clotting profiles.

The role of HRT on the bone can be summarised as follows:

1. Oestrogen is most effective in retarding bone loss when it is initiated shortly after the onset of menopause.
2. Oestrogen must be used for at least 7 to 10 years to have an effect on bone loss.[10]

Table 3: Some indications for bone mass measurement

1. Presence of strong risk factors
   - Premature menopause (< 45 years)
   - Prolonged secondary amenorrhoea
   - Primary hypogonadism
   - Corticosteroid therapy
   - Secondary causes for osteoporosis
     - Anorexia nervosa
     - Malabsorption
     - Primary hyperparathyroidism
     - Post-transplantation
     - Chronic renal failure
     - Hyperthyroidism
     - Prolonged immobilization
     - Cushing's syndrome
2. Previous osteoporotic fracture
3. Radiographic evidence of osteopenia and vertebral deformity
4. Significant loss of height or kyphosis
5. Monitoring treatment efficacy
6. Perimenopausal and postmenopausal women who are making a decision on preventive therapy based on BMD results

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3. Present oestrogen use is more important than past use. Current oestrogen users had a significantly lower risk of fractures than their contemporaries who had taken oestrogen for several years, but had discontinued it many years previously.[11] It is clear that the protective effect of oestrogen on the bone will wear off once the woman stops oestrogen.

4. Progestogen use has a minimal effect on osteoporosis risk. Women who have had a hysterectomy and are considering HRT need not add a progestin for the sake of their bones.[9]

HRT has been reported to be associated with an increased risk of breast cancer – a finding that remains controversial.[11] There was no increase in risk associated with taking HRT up to 5 years. HRT for more than 5 to 10 years increases the average woman's risk of breast cancer by 30%. The increase in risk seemed to disappear entirely 2 years after HRT was discontinued.

Selective estrogen receptor modulators (SERMS)

SERMS is a new group of agents with oestrogen agonistic action in some tissues such as the bone, cardiovascular system, brain and has antagonistic action in other tissues such as uterus and breast. The prototype of this class of drugs is tamoxifen, which is used to treat and prevent breast cancer. Interest has been generated by this class of drugs, especially in the last few years when it was realized that oestrogen binds to two receptors – α, the original receptor (present in breast, uterine endometrium, liver) and the newly identified oestrogen receptor β (present in bone, blood vessels). Because of lack of stimulatory action on the uterus, it is unnecessary to add on progestogens in women with an intact uterus.

Raloxifene has been marketed in some countries recently as an alternative to other oestrogen preparations. Like oestrogen, Raloxifene lowers LDL cholesterol, and has no adverse effect on total triglyceride, although unlike oestrogen it does not raise the HDL cholesterol level.[12] Results showed that with 24 months of treatment, clinical vertebral fractures was decreased by half.[13] Although the bone mineral density increase was modest (increased by 2.0% at the hip and by 2.5% at the spine), fracture incidence is reduced by 50% which was similar to that from HRT or other agents such as alendronate. The effect on hip fracture protection is still uncertain.

Because SERMS are selective, and act as antagonists in the breast tissue, evidence is mounting that they are not associated with breast cancer risk. With 33 months of therapy, Raloxifene lowered the risk of breast cancer by 70%.[14]

Bisphosphonates

Bisphosphonates inhibit bone resorption by binding to mineralized bone surfaces. Bisphosphonates may be considered as an alternative to HRT in postmenopausal osteoporotic women who cannot tolerate HRT. Compared with HRT, bisphospho-nates are bone specific, of equal or greater efficiency in improving bone density and have fewer side-effects.[15] The bisphosphonates are poorly absorbed and should not be taken with meals or calcium tablets. At present etidronate and alendronate are the most commonly used bisphosphonates.

Treatment with etidronate can increase the lumbar spine BMD by 5 - 10% over 2 years. Vertebral fracture risk is decreased. The effect of etidronate on hip fracture is not known. To avoid mineralization defect, etidronate is given cyclically in a dose of 400mg daily for 14 days every 3 months. Calcium supplementation is given during the rest of the 3-month cycle when the patient is not on etidronate. Side effects are uncommon.

Alendronate at a dose of 10 mg daily increased the lumbar spine BMD by 8% and the femoral neck BMD by 5% in three years.[16] In large randomised controlled trials, alendronate was shown to reduce both vertebral fracture and hip fracture in postmenopausal osteoporotic women by approximately 50% in those with and without pre-existing vertebral fractures.[17] Alendronate is prescribed at a continuous dose of 10 mg daily. At this dose it is not known to cause mineralization defect. To avoid oesophageal and upper intestinal irritation, it must be taken with a full glass of water at least 30 minutes before breakfast.

Treatment with bisphosphonates should be given for three to five years. At present it is uncertain how long the drug should be continued and whether bone loss will resume

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once the drug is stopped. Apart from postmenopausal osteoporosis, bisphonates are also useful in treating steroid-induced bone loss. There are ongoing trials to evaluate the use of bisphosphonates in treating male osteoporosis.

Calcitonin

Calcitonin inhibits bone resorption by inhibiting osteoclast activity. Small scale studies showed significant improvement in BMD in postmenopausal women.[18] Long-term effects of calcitonin on fracture prevention are not available. A large scale prospective study is currently ongoing to address this issue. Current evidence does not support its use as a first line treatment for established osteoporosis. Its use is also limited by cost consideration. Calcitonin is given either by parental injection (50 to 100 IU daily or 100 IU three times per week given intramuscularly or subcutaneously) or as a nasal spray (200 IU daily). When given parentally, calcitonin may cause nausea, flushing and gastrointestinal upset. Nasal calcitonin may result in nasal irritation.

In addition to preventing bone loss, calcitonin also has analgesic effect and can reduce acute pain associated with vertebral fractures.[19] Therapy should be adjusted according to response and may be effective for at least one month.

Vitamin D

The use of vitamin D and its derivatives in the treatment of osteoporosis is controversial. With the sufficient sunlight in Hong Kong, it is unnecessary to recommend vitamin D for everyone. For the elderly who are institutionalized may be at risk of vitamin D insufficiency, supplementation of vitamin D of 400 to 800 IU per day is recommended. It has been shown that vitamin D is not useful in preventing hip fractures in ambulatory community-dwelling postmenopausal women, but is able to reduce hip fractures in institutionalized subjects.[20-21] The use of vitamin D derivatives such as 1 α-vitamin D and calcitriol may be complicated by hypercalcaemia and hypercalciuria.

Monitoring of treatment progress

Bone mass measurements

It is recommended to repeat BMD by DXA studies at 2 yearly intervals after the initiation of treatment. Even with the best treatment and response, there will only be at most a 5-10% increase in the bone density. Treatment induced changes are often most marked at the spine. Repeated assessment is not routinely indicated in healthy perimenopausal or postmenopausal women already taking HRT for prevention of bone loss, but is justified in patients taking HRT or other anti-resorptive agents, such as bisphosphonates or calcitonin, who have complicating factors such as malabsorption or corticosteroid therapy. The BMD measured with different machines cannot be directly compared as there are significant differences among the methods used.

It is recommended to follow-up patients with calibrated machines from the same manufacturers. The use of QUS in following treatment progress awaits further validation.

Biochemical markers of bone turnover

Treatment with anti-resorptive agents in postmenopausal osteoporosis induces a 30 - 60% decrease in biochemical markers of bone turnover within 3 to 6 months of therapy. The acute response of biochemical markers to treatment is predictive of the subsequent response of the bone mass over 2 years, but the lack of response of these markers does not necessarily mean a poor response in BMD. Measurement of biochemical bone markers at baseline and after 3 to 6 months of therapy may help to improve patient's compliance, since these treatment effect can be detected much earlier than changes in BMD. At present, these biochemical tests are not widely available. ∎

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Key messages

1. The approach in the management of osteoporosis is towards early identification of high risk patients for preventive and therapeutic treatment.

2. General preventive measures include correction of treatable risk factors, such as smoking, alcohol, physical inactivity, low dietary calcium intake, and vitamin D deficiency.

3. Existence of multiple risk factors is associated with increased risk of osteoporotic fractures. Confirmation of diagnosis is by bone densitometry assessment.

4. Osteoporosis is defined as having a bone mineral density (BMD) 2.5 standard deviation below the peak young mean of the population (i.e. T-score < -2.5).

5. Therapeutic agents include hormonal replacement therapy (HRT), bisphosphonates, calcitonin and vitamin D. Calcium supplementation alone is inadequate for established osteoporosis.

6. Massive screening of BMD in healthy perimenopausal women is not indicated, especially in women who are already taking bone-sparing dose of HRT.

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