Clinical Management Guidelines for Osteoporosis in Hong Kong

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ABSTRACT

With aging of the Hong Kong population, osteoporosis has become one of the most prevalent conditions that is associated with great medical and socioeconomic burden. In view of rapid advancement in the diagnosis and treatment of the disease in the past few years, the Osteoporosis Society of Hong Kong feels the need to update the management guidelines currently available in Hong Kong. This present set of guidelines highlights the current consensus in the diagnosis and management of osteoporosis. An evidence-based account on the pharmacological treatment of osteoporosis is given. Reference is also drawn to available published data collected from local sources. These guidelines aim to provide a basis for the management of osteoporosis for the practising physicians in Hong Kong.

INTRODUCTION

Osteoporosis represents a major public health problem worldwide, and this burden is growing. The serious consequence of osteoporosis is bone fracture. In the last two decades, attention has been drawn to the importance of this disease as the case burden increases dramatically in association with aging of the world's population. In 1998, a guideline on the management of osteoporosis in Hong Kong was prepared by a group of specialists.[1] With the rapid advancement in knowledge of the pathogenesis and diagnosis of osteoporosis as well as publications of new data on treatment of the disease, an update of the guidelines has recently been prepared under the auspices of the Osteoporosis Society of Hong Kong. The main objectives of this document are first, to provide an evidence-based account of the available therapeutic interventions, and second, to offer an algorithm for the management of individual patients based on published data collected from both Caucasians and local Chinese. The guidelines were prepared mainly for primary care physicians who are the major health care providers of osteoporotic patients in Hong Kong.

EPIDEMIOLOGY

The public health impact of osteoporosis stems from its association with fractures of the hip, spine and forearm. Ten to twenty percent of hip fracture patients die within a year of the event, and of those who survive, almost two-thirds remain disabled. The medical cost of osteoporosis and its attendant fractures have been placed at US$5.2 billion each year in the US and £615 million each year in the UK.[2,3] The majority of direct cost (95%) was incurred by hospitalized patients, due to hospital and rehabilitation expenses.[4] In Hong Kong, the total cost for the treatment of hip fractures was HK$150 million in 1995. According to the report of the Hospital Authority in 1996, the acute hospital care cost of hip fractures amounted to 1% of the total annual hospital budget, or US$17 million, for a

population of 6 million.

Incidence of Hip Fracture

There is a general lack of longitudinal data on the relationship between bone mineral density (BMD) measurements, risk factors and the risk of hip fracture among Asian populations. However, cross-sectional studies demonstrated that risk factors for hip fracture are similar to Caucasian.[5] Moreover, the relationship between the relative risk of hip fracture and diminishing BMD in Hong Kong Chinese were found to be similar to Caucasians.[6] While the incidence of hip fractures were similar in young men and women, an exponential rise was seen in women from 65 years onwards and in men from 70 years onwards. The rates in elderly women were twice as high as in elderly men.[7]

In the 1960's, there was pronounced geographical variations in hip fracture incidence, with rates much higher in Caucasians living in Northern Europe and North America than in Hong Kong Chinese (Table 1).[8] In the 1960's, the age-adjusted incidence of hip fracture in Hong Kong Chinese was approximately 13 to 30% of that observed in Caucasians.[9] Recent studies indicate that the age-specific incidence of hip fracture has leveled off from 1985 to 1991 in both men and women (Table 2).[9] In 1995/6, the incidence of hip fracture was 11 per 1000 in women and 5 per 1000 in men who are 70 years and older.

There is some evidence that the incidence of hip fracture is rising rapidly in developing Asian countries. For instance, in Hong Kong, a highly urbanized city, the incidence of hip fracture had increased by 300% in women and 200% in men in the last 3 decades (Table 2).[9] A recent multi-national study conducted in four Asian countries showed the incidence of hip fracture to be directly proportional to economic development. The adjusted rates in Hong Kong and Singapore were almost identical to American Caucasians (at 19 per 10,000), while

the rates in Thailand and Malaysia were 2/3 and 1/2 of the Hong Kong rates respectively.[10]

The projected number of hip fractures in Hong Kong in future can be calculated by applying the current age-specific rates to the future population of Hong Kong. Assuming no increase in age-specific rates, the total number of hip fractures in the year 2015 will be 5,293 and 2,349 in Hong Kong women and men respectively.[9] The incidence of hip fracture in Mainland China used to be one of the lowest in the world, being 10 per 10,000 in both men and women, with rising trend from 1988 to 1992.[11] The experience in Hong Kong suggests that with socio-economic development in China, the incidence of hip fracture is likely to rise. With rapid economic development and aging of the population, hip fracture will be a major health problem in Asia. Indeed, it has been projected that, by the year 2050, more than half of all hip fractures in the world will occur in Asia.[12]

Prevalence of Vertebral Fracture

According to radiographic studies, 19-26% of postmenopausal women have a vertebral deformity.[13-16] Vertebral fractures are as frequent in Asians as in Caucasian women.[17,18] The prevalence of vertebral fracture (based on a definition of vertebral height ratio reduction by 3 standard deviations or more) has been found to be 30% in Hong Kong women and 17% in Hong Kong men who were 70-79 years old. These rates are much higher than those in Taiwan and Mainland China, and are comparable to those in American Caucasians.[18] The effects of vertebral fracture on back pain and low morale were consistently demonstrated in Chinese men and women.[19]

DIAGNOSIS OF OSTEOPOROSIS

Osteoporosis is characterized by compromised bone strength which depends on bone density and quality. A fragility fracture that occurs after minimal or no identifiable trauma may be taken as a clinical index of bone quality. As methods of measuring bone quality remain to be developed, the diagnosis of osteoporosis has to rely on BMD before a fragility fracture develops. Among the many techniques available in assessing BMD, dual-energy x-ray absorptiometry (DXA) has drawn the most attention in terms of technical development and clinical validation, and is regarded as the gold standard for diagnosing osteoporosis.[20-22]

Dual-Energy X-Ray Absorptiometry and Diagnostic Considerations

DXA has the advantages of very low radiation dose (comparable to an average daily dose from background radiation), short scanning time and good precision. It measures BMD in gram per cm^2, defined as the integral mass of bone mineral per unit projected area.

The widely adopted diagnostic criteria were recommended by the World Health Organization (WHO) in 1994 based on BMD measurements of the spine, hip or forearm from epidemiological studies on postmenopausal Caucasian women (Table 3).[23] BMD measurement is expressed in standard deviation (SD) units called the T-score, which is the difference between the measured BMD and the mean of a young healthy adult (peak bone mass) reference population, matched for gender and ethnicity, and normalized to the SD of that population (Equation 1). The definitions of osteoporosis, osteopenia and normal based on the T-scores intend to identify patients with high, intermediate and low fracture risks respectively.[23] In general, the relative risk of fracture would be increased by 1.5–3.0 times for each 1.0 SD decrease in BMD. Local study also demonstrated similar relationship between BMD and the risk of hip fracture.[6]

Z-score is a similar concept to the T-score, but comparison is made to a healthy age-, gender- and ethnicity-matched population (Equation 2). The Z-score is not used to define osteoporosis. It is useful in identifying individuals with BMD lower than expected for their age, and in determining facture risks compared to their peers. Low Z-scores (<-1.0) should prompt a search for secondary causes of osteoporosis.

Equation 1.

$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult population mean BMD}}{\text{Young adult population SD}}$$

Equation 2.

$$\text{Z-score} = \frac{\text{Measured BMD} - \text{Age-matched population mean BMD}}{\text{Age-matched population SD}}$$

The current recommended sites for a DXA scan are the hip and the spine since fractures at these sites carry the greatest morbidity and mortality, and BMD measurements at these sites of interest are the best predictor of fracture risk of the corresponding sites.[21,24]

Although the WHO definitions are widely applied, there are limitations and controversies. The T-score diagnostic criteria apply only to BMD measurements of the spine, proximal femur or forearm and cannot be indiscriminately applied to other skeletal sites or other technologies such as ultrasound or computed tomography. The cut-off value for T-scores at -2.5 in diagnosing osteoporosis was derived from fracture risks of postmenopausal Caucasian women, and controversy exists as to whether the same criteria can be applied to other groups such as men or non-Caucasians. In addition, there can be poor concordance of measurements and diagnostic categories between different skeletal sites owing to accuracy

errors and biological variability. Different machines can also give different BMD measurements even for the same skeletal site as a result of using different measuring algorithms. Even with the same BMD, different machines can yield different T-scores since different reference population databases are provided by vendors.[20]

The International Osteoporosis Foundation (IOF) has therefore recently made a recommendation to reserve the WHO definition or the T-score diagnostic criteria to the total hip BMD measurement only, and to use the large third US National Health and Nutritional Examination Survey (NHANES III) reference database derived from women aged 20–29 as a standardized international hip reference.[25] It is also important not to equate diagnostic thresholds with intervention thresholds, the latter should take into account the fracture risk which is multifactorial and not solely defined by BMD T-score of the hip or a diagnosis of osteoporosis *per se*. A comprehensive assessment of fracture risk requires integration of individual clinical information and factors influencing the bone mass or quality, risk of falls, available biochemical indices of bone turnover, and any densitometric or ultrasonic evaluation of other skeletal sites.

Other Diagnostic Techniques

Quantitative ultrasonography (QUS) of the calcaneum is a non-invasive, portable, inexpensive and radiation-free technique.[26] It does not measure BMD like the DXA scan, but measures other parameters (broadband ultrasound attenuation and speed of sound) to help predict the fracture risk in postmenopausal women. The T-score measured by QUS is not equivalent to that of DXA measurement and should not be used interchangeably. Moreover, the correlation of QUS parameters with BMD measurements by DXA is relatively poor. Though QUS parameters have been shown to predict hip and spine fractures in postmenopausal women,[27,28] data on its use in premenopausal women are still limited. Given

the present limited precision of QUS, it should not be recommended as a tool for monitoring bone loss or treatment response. It is advised that subjects who are shown to be osteoporotic by QUS should be validated by a formal DXA study. Despite its easy availability, indiscriminate use of QUS is discouraged.

Quantitative computed tomography (QCT) gives a measure of the volumetric BMD in gram per cm^3 of trabecular bone rather than an areal density as in the case of DXA. As trabecular bone is more responsive than cortical bone to treatment interventions, QCT of the spine can be used for monitoring purpose. Nevertheless, its use is limited by the higher precision error, radiation dose and cost. It may be considered when there is significant degenerative changes and deformities making the assessment of the spine by DXA suboptimal. However, data on normal ranges for QCT measurements are not available locally.

Other techniques such as single or dual photon absorptiometry and single x-ray absorptiometry have largely been replaced by DXA. Plain radiograph should not be used to assess bone density owing to its low sensitivity. However, plain radiograph of the spine is useful in detecting subclinical vertebral fracture (accounting for up to two-thirds of all vertebral fractures) which not only indicates the severity of disease but also serves as a strong risk factor for subsequent fracture.[29] Vertebral fracture can be defined as a 20% loss of height when compared to measurements of vertical height of anterior, mid-position and posterior margin of a vertebral body, or the corresponding measurement of the adjacent vertebral body in a lateral spine x-ray. An alternative is to have a DXA machine capable of forming a high-resolution lateral image of the spinal column for concomitant evaluation at the time of BMD measurement.

Identification of Secondary Causes of Osteoporosis

Once osteoporosis is diagnosed, it would also be important to identify any underlying secondary causes (Table 4). It is particularly relevant in male subjects since the Caucasian experience suggests that up to 50% of male osteoporotic subjects have a secondary cause.[30,31] A comprehensive history taking and physical examination can offer clues to possible causes. For routine investigations, it is reasonable to have a complete blood count, erythrocyte sedimentation rate, general biochemistry including alkaline phosphatase, serum calcium and phosphate. Thyroid function and urinary calcium excretion should also be performed. Testosterone level should be performed in men. Other special tests including serum protein electrophoresis, parathyroid hormone and 25-hydroxyvitamin D may be appropriate if the history and initial workup suggest a related disorder.

RISK IDENTIFICATION OF OSTEOPOROSIS

Osteoporosis is usually asymptomatic until a fracture occurs and consequently, it is only diagnosed in most patients after a fracture. Since there is no convincing evidence for the benefit of population-based screening,[32] an increase in awareness to identify high-risk patients remains the strategy to adopt. Case-finding is an appropriate exercise for family physicians to undertake and to diagnose the condition before a fracture occurs. Case-finding can begin by identifying patients with clinical risk factors (Table 5), medical conditions associated with osteoporosis (Table 4) and an X-ray finding of osteopenia.

The clinical risk factors listed in Table 5 however do not all carry the same weight. A history of fragility fracture and loss of height appear to have the highest predictive values. Studies have shown a seven to eight fold increase in risk of future fracture for a woman with pre-existing vertebral fracture.[29] The other clinical risk factors apply to a much larger sector of the population. In the absence of a history of fragility fracture or loss of height, it is

difficult to offer evidence-based advice about particular combinations of risk factors which should justify further investigations in postmenopausal women. In general, there seems to be an additive effect of risk factors i.e. presence of more risk factors means higher risk. A useful clinical tool to help selection of postmenopausal women for screening is the Osteoporosis Self-assessment Tool for Asians (OSTA) (Fig. 1) which has been validated in a number of Asian regions including China, Hong Kong, Japan, Korea, Malaysia, Singapore and Taiwan.[33,34] Applying this simple tool in the office, all women of the high-risk category should be recommended for BMD measurements (Table 7). For women falling into the moderate risk category, other risk factors should be actively sought to determine the need for BMD measurement. The prevalence of osteoporosis is low in the low risk category so that BMD measurement is probably not necessary. All women with a history of fragility fracture should be offered BMD measurement and considered for treatment irrespective of the OSTA values.

The medical conditions listed in Table 4 have been found to be associated with an increased risk of osteoporosis. Studies have documented significant bone loss in hypogonadal subjects and in patients receiving steroid treatment for more than three months.[35] Early DXA should be considered for these subjects irrespective of gender and menopausal status. For other medical conditions such as hyperthyroidism and hyperparathyroidism, treatment of the primary cause is important. Doctors should be more vigilant on life-style modification to prevent bone loss especially for premenopausal women. Early DXA screening should be considered when these high risk women reach their menopause. For men, the decision for early screening depends on the presence of concomitant risk factors.

PREVENTION OF OSTEOPOROSIS

Prevention of osteoporosis is best achieved with a “population approach” targeting at the

adolescents before their accretion of peak bone mass. Programs to increase public awareness are especially effective. Lifestyle changes, notably avoidance of smoking and alcoholism, should be emphasized.

Calcium

Adequate calcium intake has been documented in numerous studies to increase BMD during skeletal growth and to prevent bone loss and osteoporotic fractures in later life. However, local studies found a much lower calcium content of around 400 mg per day in Chinese diet when compared to the Western diet.[36,37] General consensus states that the recommended daily calcium intake should be around 1000 mg for adult. Calcium contents of some common food are shown in Table 6. For people who cannot tolerate milk or milk products, calcium can be taken in the form of calcium tablets. In general a 500 mg elemental calcium tablet daily is adequate for prevention of excessive bone loss. Studies have shown that calcium supplementation in postmenopausal women results in a BMD 1 to 3% higher than without supplementation and reduces fracture rates by up to 10%.[38,39] For adolescents, higher intake of calcium has been shown to improve the peak bone mass.

Vitamin D

Adequate amount of vitamin D is necessary for optimal calcium absorption and bone health. Vitamin D insufficiency causes secondary hyperparathyroidism and results in an increased bone turnover and bone loss especially at the cortical sites. Vitamin D can be considered as adequate when the serum PTH concentration is not elevated and when serum PTH does not decrease with vitamin D supplementation.[40] Chief dietary sources of vitamin D include cereals, liver, egg yolk and salt-water fish. Since there is ample sunlight in Hong Kong, it is not necessary to recommend universal vitamin D supplementation. For those who are at risk of vitamin D deficiency e.g. institutionalised elderly, supplemental vitamin D of

400 to 800 IU per day is recommended.[41] Prevalence of vitamin D insufficiency has been reported to be 60 to 80 % in the institutionalised elderly.

Exercise

There is strong evidence that physical activity early in life contributes to higher peak bone mass. Resistance and high impact exercises are likely the most beneficial. Weight-bearing exercises at time of middle age probably has a modest effect on slowing the decline in BMD. On the other hand, exercise in the elderly has minimal effect on BMD[42] but exercise can increase muscle mass and strength, improve function and contribute to better quality of life.[43] Weight-bearing and muscle-strengthening exercises can in addition improve agility, strength and balance reducing the risk of falls. On the other hand, immobilization accelerates bone loss and it should be avoided in elderly people if possible. Exercise should be recommended for all age groups both for osteoporosis prevention and overall health benefit.

Weight-bearing exercises include walking, jogging, stair-climbing and dancing. High impact weight-bearing exercises are not recommended for elderly since many of them have concomitant osteoarthritis. A number of traditional Chinese exercises are low impact weight-bearing exercises and among these, Tai-Chi has been shown to improve balance and reduce incidence of falls and fall-related injuries.[44] Muscle-strengthening exercises include weight lifting and other resistive exercises targeting at specific muscle groups such as the quadriceps.

Phytoestrogens

Phytoestrogens are natural chemicals found in plants. The two main classes that are of health interest are isoflavones and lignans. Isoflavones are available in beans and soya

products like soya milk or tofu. Lignans are found in ryes, berries, fruits, vegetables and whole grains. Extracted phytoestrogens are also marketed as dietary supplements. Although local studies have found positive effects of phytoestrogens on BMD and bone markers,[45-47] there is no consistent evidence that they offer a beneficial effect on bone density and there is no clinical evidence that phytoestrogens in any form reduce the risk of osteoporotic fractures.[48]

Fall Prevention

One of the most serious consequences of fall in an osteoporotic subject would be a fracture. A local study revealed that 18% of elderly aged 70 and above reported a history of falls, 6% of which resulted in fracture. Another report from the Elderly Health Services of the Department of Health published in 2003 identified female gender, history of repeated falls, musculoskeletal problems, urinary incontinence, depressive moods and poor financial conditions as the most important risk factors for fall.[49] Studies have also demonstrated that falls are preventable and an active approach should be adopted. Fall prevention should receive as much attention as drug therapy for osteoporosis.

Medical risk factors predisposing the elderly to fall should be identified and treated early. Visual assessment is important as impairment of vision is an important risk factor for fall. Cataract is the commonest and a correctable cause in the elderly. Hearing impairment should also be assessed. Neurological conditions such as Parkinson's disease and stroke need to be evaluated and treated appropriately. Medications need to be reviewed regularly to avoid side-effects that may affect balance and stability. Postural hypotension due to over-energetic treatment of hypertension should be avoided. Sedative and hypnotic drugs should be prescribed with special caution in the elderly. Diuretics should be kept to the minimum doses in patients with urge incontinence.

Fall prevention education programs are also important. Home and environmental safety should be emphasized. Adverse environmental hazards like poor lighting and slippery or irregular floor surfaces should be corrected. Non-slip shoeware should be encouraged. Caregivers should be educated on the correct technique in the transfer of elderly to avoid fall and fall-related injuries.

Elderly people with risk factors for or known history of fall should be assessed by physiotherapists and occupational therapists for proper training and rehabilitation. An appropriately prescribed exercise program is important for the elderly to prevent immobilization, reduce bone loss and promote muscle strength and balance. Elderly with balance problems should be prescribed appropriate walking aids and gait-training exercises.

Through its beneficial effects on neuromuscular function, medical treatment with vitamin D and its active metabolites have been reported to be able to decrease the risk of fall. A recent meta-analysis revealed that vitamin D supplementation appeared to reduce the risk of fall among ambulatory or institutionalized elderly with stable health by more than 20%. Subgroup analyses suggested that the effect size was independent of calcium supplementation, type of vitamin D, duration of therapy and sex.[50] Further studies are required for more general recommendation of its use in fall prevention.

For elderly with a history of recurrent fall or fractures, hip protectors have been found to be useful in the prevention of future hip fractures but their effectiveness is limited by a low degree of acceptance and compliance. An acceptance rate ranging from 37 to 72% while compliance varied from 20 to 90% was reported in the literature.[51] Reasons for not wearing hip protectors include discomfort, extra time needed to wear the device, urinary incontinence

and physical difficulty or illnesses. A local study showed that compliance with hip protectors varied from 55 to 70% and hip protectors achieved an 82% reduction in the risk of hip fracture.[52]

PHARMACOLOGICAL TREATMENT OF OSTEOPOROSIS

In general, pharmacological treatment should be seriously considered in postmenopausal women with a history of low fragility fracture or significant loss of height. A BMD measurement by DXA should be performed to provide the baseline for monitoring the efficacy of treatment. Postmenopausal women with a BMD T-score of -2.5 and below should also be considered for pharmacological treatment. For postmenopausal women with BMD in the range of osteopenia, the threshold to start pharmacological treatment will depend on the presence of other risk factors.

Calcium, Vitamin D3 and Hydroxylated Vitamin D

Studies using calcium as monotherapy reported variable results because of the differences in the studied populations, treatment doses and the small sample size of most studies. In general, calcium supplementation can increase BMD by about 1.5% and probably reduce vertebral fracture rate by 20%.[38,39,53-55]

For vitamin D supplementation, a study in a group of community dwelling elderly reported that combination of 700 U vitamin D3 and 500 mg calcium resulted in an increase in BMD and a reduction of total number of non-vertebral fractures, but in this study, only one hip fracture occurred in the placebo group.[56] On the other hand, a study in a group of institutionalized elderly reported that combination of 800 IU vitamin D3 and 1.2 g calcium increased BMD by about 6% and reduced hip fracture by about 40%.[41] In general, vitamin D3 and calcium are recommended for institutionalized but not for community dwelling elderly

for the prevention of fractures.

In addition, vitamin D3 or hydroxylated vitamin D (alfacalcidol or calcitriol) with or without calcium appears to decrease the risk of fall among ambulatory or institutionalized elderly by about 20%.[50] Hydroxylated vitamin D (alfacalcidol or calcitriol) with or without calcium probably reduced vertebral fractures whereas its effect on reducing non-vertebral fractures was uncertain.[57]

It should be noted that almost all subjects in all the landmark trials to determine the efficacy of various anti-resorptive agents on fracture reduction had received calcium supplementation in the dose range of 500 to 1000 mg daily with or without vitamin D3 250 to 600 IU daily. In general, it is recommended to prescribe calcium and/or vitamin D3 when starting on anti-resorptive agents unless there are contraindications.

Hormonal Replacement Therapy (HRT)

The beneficial effect of estrogen on bone mass has been clearly demonstrated in prospective, double-blind controlled studies. Epidemiological evidence indicated that women exposed to estrogen therapy for more than 7 years have a 50% lower chance of osteoporotic fractures than non-users.[58]

In 2002, the Women's Health Initiative (WHI), a prospective, randomized, placebo-controlled, double-blind multicentre study involving over 16,000 postmenopausal women in the United States showed a 33% reduction in vertebral fractures, a 33% reduction in hip fractures and an overall 24% reduction in any fractures with HRT (specifically conjugated equine estrogen 0.625 mg plus medroxyprogesterone 2.5 mg daily) compared with placebo over 5.2 years.[59,60] The same study also showed significant increase in the risks of heart attacks, strokes, pulmonary emboli and breast cancers. It concluded that the overall

balance of risks and benefits of HRT was unfavourable.

Despite the early termination of the WHI trial in patients on combination therapy, the estrogen-only arm was continued until March 2004, when the National Institutes of Health (NIH) also stopped the study in the interest of safety after finding an increased risk of stroke.[61] The magnitude of the increase in the risk of stroke was similar to that found in the previous report on patients taking estrogen plus progestin. However, there was no apparent increase in the risk of breast cancer and ischaemic heart disease. A decrease in the risk of hip fracture was again confirmed. It is now recommended that the use of HRT is limited to the treatment of moderate to severe climacteric syndrome and short-term prevention of osteoporosis in the early menopausal period. For osteoporosis prevention, other modalities of intervention should be carefully considered.

In conclusion, HRT is no longer the first-line treatment for treatment of osteoporosis.

Bisphosphonates

Bisphosphonates are bone-specific agents with greater efficacy in improving bone density and have fewer side-effects compared to HRT. Bisphosphonates inhibit bone resorption by binding to the mineralized bone surface. These compounds are poorly absorbed from the gastrointestinal tract and should not be taken with meals or calcium tablets. For optimal absorption, they should be ingested on an empty stomach, either first thing in the morning after an overnight fast with avoidance of food for 30 minutes afterwards, or in the middle of a four-hour fast. They should be washed down the esophagus with a large glass of water. Etidronate was the first generation drug to be used. Alendronate and risedronate are both nitrogen-containing derivatives that are a hundred to a thousand times more potent than etidronate, and are effective in inhibiting bone resorption without causing mineralization

defects. They can on rare occasions give rise to esophageal ulceration. The risk can be reduced by the avoidance of lying flat within 30 minutes of ingestion or by using the once weekly preparation taken with the same precautions.

It is likely that the beneficial effects on fracture reduction and gain in BMD are a class effect. Well-designed direct head-to-head comparison studies between alendronate and risedronate are not available. The selection of a specific drug for an individual patient is at the discretion of the prescribing physician, taking into account the overall patient's health status, affordability, tolerability and patient preference.

(i) Etidronate

Treatment with etidronate can increase the lumbar spine BMD and decrease the vertebral fracture risk by 37%. The effect of etidronate on hip fracture is not known. To avoid mineralization defect, etidronate is given cyclically at a dosage of 400 mg daily for 14 days every 3 months. It has to be administered in the middle of a 4-hour fast. Calcium supplementation is given during the rest of the 3-month cycle when the patient is not receiving etidronate.

(ii) Alendronate

Alendronate therapy has been shown in prospective, randomized, double-blind and placebo-controlled trials to prevent bone loss and increase BMD at the spine and hip by 5-10%.[62-64] Local studies have shown a comparative increase in BMD of 5.8% at the lumbar spine and 3.4% at the hip, after one year treatment of alendronate in postmenopausal osteoporotic Chinese women.[65,66] According to the latest meta-analysis involving 12,855 patients, alendronate reduced the relative risk of vertebral fracture by 50%.[67] In six randomized studies (3723 patients), it also reduced the incidence of lower arm and

non-vertebral fractures by approximately 50%. With regard to hip fracture, the collated data of 11 studies showed that alendronate treatment resulted in a 40% reduction in fracture risk. However, it should be noted that the effects were only significant in patients with a BMD T-score below -2.5. These studies covered follow-up periods of up to 4 years. The more recent data confirmed the effectiveness of alendronate after 10 years of monitoring.[68] The effects of alendronate on BMD at the spine and hip were maintained for at least 2 years after discontinuation. Alendronate has also been shown to be effective in increasing BMD in males[69,70] and subjects with glucocorticoid-induced osteoporosis.[71]

Alendronate is prescribed either at a daily dose of 10 mg or a weekly dose of 70 mg.[72] The tablet must be taken with a full glass of water at least 30 minutes before breakfast. One has to stay in the erect posture for at least 30 minutes after drug administration. Side effects of alendronate include upper gastrointestinal symptoms such as heartburn, indigestion and retrosternal pain. Rare occurrences of esophageal erosion and ulceration have been reported. Contraindications include hypersensitivity to alendronate, hypocalcaemia and esophageal abnormalities such as stricture or achalasia. It should be used with caution in patients with renal impairment.

(iii) Risedronate

After 1.5 to 3 years of therapy with risedronate, the pooled estimate of treatment effect was 4.5% increase in BMD of the lumbar spine and about 3% in the femoral neck.[73-75] At a dose of 5 mg daily, it reduces the risk of fractures of the spine and hip by 30 to 50%. Pooled results revealed that risedronate significantly reduced clinical vertebral and non-vertebral fractures as early as six months after initiation of treatment in patients with osteoporosis.[73] Risedronate was mainly effective in patients with BMD T-score below -2.5. Seven years' data continued to demonstrate anti-fracture effect with a safety profile similar to placebo.

Risedronate has also been shown to preserve bone mass and reduce the incidence of vertebral fractures in glucocorticoid-treated patients.[76] Risedronate can also be taken weekly at a dose of 35 mg.

The mode of administration and contraindications of risedronate are similar to those of alendronate. Whether the gastrointestinal tolerability is different is not known. Post-marketing experience suggests satisfactory gastrointestinal tolerability.

Selective Estrogen Receptor Modulator (SERM)

Selective estrogen receptor modulators activate estrogen receptors in target organs selectively to produce quantitatively variable estrogenic effects on estrogen-responsive tissues. Raloxifene hydrochloride, a benzothiophene derivative, is a non-hormonal agent that binds with high affinity to the estrogen receptor and exhibit estrogen-agonistic effects on bone and estrogen-antagonistic effects on the endometrium and breasts. Raloxifene increases BMD in the spine by 2.7% and in the femoral neck by 2.4% over placebo, and reduces bone turnover to premenopausal levels.[77] Its efficacy on increasing BMD and suppressing biochemical markers of bone turnover as well as safety has been confirmed in healthy postmenopausal Asian women.[78] Among postmenopausal women with osteoporosis studied for 36 months, raloxifene at a dose of 60 mg daily reduced the risk of vertebral fractures by 30 to 50%.[79] There was no significant reduction in the risk of hip fractures.

In addition, raloxifene has extra-skeletal beneficial effects. It reduces total cholesterol and low-density lipoprotein cholesterol by about 7 and 11% respectively. In the Multiple Outcomes of Raloxifene Evaluation (MORE) Study of 5,129 postmenopausal women with osteoporosis treated with raloxifene for 4 years, a 72% overall reduction of breast carcinoma and a 84% reduction in estrogen receptor-positive breast cancers were noted in comparison

with placebo.[80,81]

Side-effects include hot flushes, leg cramps, fluid retention and a three-fold increase in the risk of venous thromboembolic diseases in Caucasians.

Calcitonin

Salmon calcitonin is prescribed as a nasal spray of 200 IU daily or as subcutaneous injections. In the acute stage following an osteoporotic fracture, the injectable form may be prescribed for its analgesic property.[82] During the 5-year PROOF study, a significant 36% reduction in vertebral fracture risk was shown only in the group treated with 200 IU of intra-nasal calcitonin daily.[83] Risk reduction in non-vertebral fractures was not significant at any of the doses tested. Calcitonin is therefore mainly recommended as an alternative to bisphosphonates or SERMs when they are not tolerated or contraindicated. Side-effects include rhinitis, irritation of the nasal mucosa, epistaxis and anaphylaxis reaction.

Summary of Anti-Resorptive Therapies for Postmenopausal Osteoporosis

	HRT	Raloxifene	Calcitonin	Etidronate	Alendronate	Risedronate
BMD Spine	↑	↑	↑	↑	↑	↑
BMD Hip	↑	↑	→	↑	↑	↑
Biochemical markers	↓	↓	↓	↓	↓	↓
Spine Fracture	↓	↓	↓	↓	↓	↓
Hip Fracture	↓	→	→	→	↓	↓

Other Therapeutic Agents

Thiazides

Thiazides are effective in reducing urinary calcium excretion. Epidemiological studies showed fracture risk reduction in patients treated with thiazides. However, it has not been validated by double-blind, placebo-controlled studies. In osteoporotic patients with hypertension and renal hypercalciuria, it is worthwhile to prescribe thiazides as an anti-hypertensive therapy.

Teriparatide (Recombinant-Human Parathyroid Hormone (PTH) 1-34)

PTH analogs are the first genuinely anabolic agent for the treatment of osteoporosis. Intermittent daily injection of teriparatide (1-34 PTH) increases BMD by more than 10% at the lumbar spine and 3% at the hip in osteoporotic female with prior history of vertebral fractures. It is capable of reducing the risk of vertebral and non-vertebral fractures by 65% and 54% respectively in postmenopausal female.[84] The same increase in BMD was also found in patients with male osteoporosis[70] or glucocorticoid-induced osteoporosis.[85] The recommended dose of teriparatide is 20 mcg daily injected subcutaneously. Side-effects are mild and transient and include nausea and orthostatic hypotension. Transient asymptomatic hypercalcaemia has also been observed. Two-year is the maximum recommended treatment duration because of studies showing an increased risk of osteosarcoma in rats with prolonged high dose therapy.

Strontium Ranelate

Strontium is a trace element that has been shown to stimulate the formation of osteoid tissue and repress the resorptive processes in bone. It is being investigated in a large phase-3 program initiated in 1996 that includes two extensive clinical trials for the treatment of severe

osteoporosis.[86,87] The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial assesses the effect of strontium ranelate on the risk of vertebral fractures. The Treatment of Peripheral Osteoporosis study (TROPOS) evaluates the effect on peripheral fractures. Preliminary report showed that treatment with oral strontium ranelate at a dose of 2 g daily reduced the risk of new vertebral fractures by 41% as compared with placebo.[88]

Testosterone Replacement Therapy in Men

Testosterone replacement is prescribed either via the oral route or as intra-muscular injections of testosterone esters once every two to four weeks. Local data showed that the prevalence of clinical and morphometric fractures was up to 19% in Chinese male with hypogonadism and osteoporosis.[89] Testosterone replacement therapy increased BMD by 5.9% at the lumbar spine and 2% at the hip annually over the first two years of treatment.[89] The increase in BMD was independent of the etiology of hypogonadism. Patients with the lowest BMD at baseline achieved the greatest increase with therapy. However, data on prevention of fractures are lacking. Efficacy of testosterone in eugonadal men has not been proven.

Side-effects include increase in haemoglobin, decrease in HDL level, acne and pain due to intra-muscular injections. The prostate increases to the size of age-matched controls but does not continue to grow with continuing replacement therapy. Breast tenderness and sleep apnoea are occasionally seen. Testosterone is contraindicated in men with prostate cancer.[90]

Indications for Referral to Specialist Care

Referral to a specialist should be considered if the patient meets one of the following criteria:

1. Osteoporosis at young age (pre-menopausal)

2. Unexpectedly low T-score (< -3.0) or disproportionately low Z-score (< -2.0)
3. Suspected or known underlying diseases (e.g. hyperthyroidism, hyperparathyroidism, hypercalciuria, Cushing's syndrome, hypogonadism or steroid therapy)
4. Candidates for anabolic therapies
5. Intolerance to anti-resorptive therapies
6. Failure to respond to treatment as evidenced by continuing bone loss or fracture development while on treatment
7. Physician indecisive for treatment

Cost-Effectiveness in Treatment of Osteoporosis

Local data for the absolute risk of fractures are required in order to calculate the cost-effectiveness of treatment. We are still lacking data to accurately model the cost-effectiveness of treatment of osteoporosis in Hong Kong. However, according to Caucasian data on the number of patients needed to treat (NNT) to prevent a major fracture, treating osteoporosis is as effective as treating hypertension or dyslipidaemia to prevent one death due to stroke or myocardial infarction (MI). The 5-year NNT to prevent one major event (MI, stroke or death) with anti-hypertensives (including diuretics, beta-blocker, angiotensin converting enzyme inhibitor, alpha-blocker or calcium channel blocker) was 86 for middle-aged patients and 29 for elderly patients.[91] In six trials on primary prevention with lipid-lowering agents, the NNT was 53 to prevent a non-fatal MI and 190 to prevent all-cause death (4.8 years of treatment with total cholesterol reduction of 15%).[92] For osteoporosis, in a meta-analysis of treatment in postmenopausal patients, the NNT in the high-risk population with low BMD to prevent a vertebral fracture over a period of 2 years were 72, 96, and 99 for alendronate, risedronate and raloxifene respectively.[93] For prevention of any one non-vertebral fracture, the NNT for alendronate and risedronate were 24 and 43 respectively.[93] The NNT would be expected to be smaller for subjects of higher risk or for treatment over

longer periods of time. However, the NNT for different therapeutic agents cannot be directly compared since there are differences in patient characteristics and study methodology. So the conclusions about the relative effectiveness of different osteoporosis therapies must await results of direct head-to-head comparison in randomized trials.

MONITORING OF OSTEOPOROSIS TREATMENT

Non-compliance to therapy remains the most important concern in treatment of chronic diseases including osteoporosis. One study reported that only 35% of women remained on alendronate treatment after 6 months.[94] During follow-up visits, drug compliance and adherence to lifestyle modifications should be monitored and reinforced. Adverse drug effects should be detected and dealt with effectively. A recent study showed that simple follow up interviews by nursing staff could significantly increase adherence to therapy by 57% when compared with usual care.[95] Osteoporosis is largely an asymptomatic condition and it cannot be overemphasized that a high degree of patient motivation and physician commitment are pivotal to its effective management.

Serial Bone Density Measurements

The ultimate end-point of anti-osteoporosis therapy is the reduction of the incidence of fractures. While BMD measurement is critical to the diagnosis of osteoporosis, the value of serial densitometry in the monitoring of therapy in individual patients is a subject of controversy.[96]

In clinical studies, it has been shown that patients with larger increase in BMD during anti-resorptive therapy had a lower incidence of new vertebral fractures.[97] A meta-analysis of anti-resorptive therapy showed that larger increase in BMD was significantly associated with greater reduction in non-vertebral fracture risk.[98] Therefore it appears logical to measure

changes in BMD as a surrogate marker for effectiveness of therapy.[96,99] The spine being the most metabolically active part of the skeleton is the most sensitive site for monitoring changes in bone density.

One significant limitation in serial BMD measurements relates to its precision error. Long-term precisions of 1.1%, 1.3% and 2.2% have been obtained for the lumbar spine, total hip and femoral neck BMD respectively.[100] To detect changes at the 95% confidence level they have to be at least 2.8 times the precision error.[101] As most of the current therapies for osteoporosis can only raise the BMD by 5 to 10% in 2 to 3 years, follow-up measurements of BMD by DXA studies are generally performed when patients have received treatment for at least two years. Baseline and follow-up BMD measurements should be performed with the same machine to minimize measurement errors.[102]

In addition, it should be noted that fracture reduction cannot be explained by increase in BMD alone.[103,104] Hitherto, there has not been any randomized trials comparing different monitoring intervals or monitoring versus no monitoring, nor is there sufficient evidence to show that changes in treatment based on serial BMD measurements result in improved patient outcome.[103]

The decision to repeat BMD measurement should be individualized. Patients who are found to have decrease in BMD despite treatment should be evaluated for compliance or the presence of secondary causes for osteoporosis.

Monitoring response to anti-osteoporosis therapy using calcaneal ultrasonometry is not recommended as there is poor correlation between changes in calcaneal parameters and the BMD of the lumbar spine and femoral neck.[105]

Biochemical Markers of Bone Turnover

Biochemical markers of bone formation and resorption provide information on the rates of bone turnover. Higher levels are associated with faster and possibly greater bone loss. Currently there is no role for them in the diagnosis of osteoporosis as there is substantial overlap in values for normal and osteoporotic subjects.[106,107] However, they have prognostic values in predicting future risk for bone loss and in the monitoring of efficacy of anti-resorptive therapy in patients with osteoporosis[98]. Unexpected high levels of markers should also raise the suspicion for other disorders associated with high bone turnover such as hyperthyroidism, hyperparathyroidism, Paget's disease and osseous metastases.

Commonly measured markers of bone formation include serum osteocalcin and serum bone-specific alkaline phosphatase while markers for bone resorption include serum type I collagen cross-linked N-telopeptide (NTX), serum type I C-telopeptide breakdown products (CTX) and urinary NTX, CTX and free deoxypyridinoline. Serum CTX appears to be the most sensitive marker among them.[106]

(i) Clinical Use in Predicting Risk for Future Bone Loss

A single measurement of BMD, though important in the prediction of current fracture risk, does not predict the subsequent rate of bone loss. Information for the latter may be obtained by measurement of biochemical markers of bone turnover. Higher levels of bone formation and resorption markers have been shown to be associated with significantly faster and greater subsequent bone loss in population studies. They have the potential to help clinicians to identify fast bone losers for whom prompt intervention may be needed.

(ii) Clinical Use in Monitoring Response to Anti-Osteoporosis Therapy

As discussed, early response to anti-resorptive therapy cannot be reliably assessed by BMD measurements. Early response may however be obtained by measurements of biochemical markers at baseline and after three to six months of therapy. For anti-resorptive therapy, a 30 to 60% decrease from baseline values generally provides evidence of efficacy and this may help in reinforcing patient compliance. In contrast, during anabolic therapy such as teriparatide, biochemical markers of bone formation increase early in the course of therapy and are followed by increase in markers of resorption.[108]

In conclusion, use of biochemical markers in monitoring of anti-osteoporosis therapy in individual patients is still limited by high intra-individual and diurnal variability[109] as well as their limited availability. However, significant progress in the development of new and more sensitive and specific markers is rapidly emerging and may alter our future practice.

MANAGEMENT OF OSTEOPOROTIC FRACTURES

Hip Fracture

Since operative treatment of elderly hip fractures can result in improved rehabilitation, this should be the preferred treatment. The operation should be performed within 24-48 hours of admission after essential pre-operative workup. While prophylactic antibiotic cover must be provided, it remains an individual practice to administer anticoagulation for the prevention of deep vein thrombosis.

Numerous studies on hip fracture fixation have been published and the sliding hip screw is still the implant of choice for most intertrochanteric fractures. As regards femoral neck fracture, either hemi-arthroplasty or screw fixation can be considered, depending on the extent

of fracture displacement.

Vertebral Fracture

A painful consequence of osteoporosis is a compression fracture of a vertebral body. Vertebral fractures can lead to acute and chronic pain, physical deformities, respiratory compromise and emotional trauma. Most osteoporotic vertebral compression fractures can be treated non-surgically. Pain relief can sometimes be obtained with morphine and other potent analgesics. Calcitonin can also be used as an adjunct.[82]

New surgical advances in treating vertebral compression fractures are evolving. Percutaneous vertebroplasty, which involves the percutaneous injection of bone cement directly into the fractured vertebral body, is effective in the treatment of patients with persistent painful vertebral compression fractures.[110] Good early clinical results with low complication profiles have been reported. Open surgery, although enormously challenging because of the poor underlying health status and structurally weak bone, may be the last resort for a small percentage of patients who experience progressive deformity or neurological deficit.

Wrist Fracture

Although most distal radial fractures in the elderly can be effectively treated by casting, there are other surgical options including external fixation and internal fixation. The choice is usually based on the fracture configuration and stability. Moreover, as more elderly people are enjoying a more active lifestyle, the physical demand of the patient must also be taken into consideration. One should always remember that significant wrist deformities can lead to real sufferings.

REHABILITATION OF OSTEOPOROTIC FRACTURES

General Principles

To ensure comprehensive and efficient rehabilitation of patients suffering from fracture and osteoporosis, a multi-disciplinary team approach in the management is crucial. Realistic and practical goals should be set in the early phase of management. Exercise prescription, like medications, has to be individualized and monitored. Both aerobic and muscle strengthening exercises can enhance cardiovascular fitness, improve balance, decrease the risk of fall, improve posture, increase flexibility of soft tissues, decrease depression and generally provide a better quality of life. Forward bending and twisting of the spine such as sit-ups, stomach crunches and toe touches generate high compression loads on the vertebral bodies and should be avoided.

Slow-movement martial arts, like Tai-Chi, have been shown to be effective not only in reducing the risk of falls, but also in maintaining bone mass and strength.[44]

Early mobilization is beneficial in the rehabilitation of patients with hip or vertebral fractures. Prolonged bed rest has deleterious effects on the functional return in the elderly.

Hip Fracture

Fall appears to precede about 90% of hip fractures. Comprehensive medical and occupational assessment including home assessment can reduce the risk of subsequent fall. Hip protectors are useful in reducing the risk of hip fracture as evidenced by local and overseas studies.[51,52] However, low compliance is a major drawback of this device. Prescription of walking aids is required in the majority of cases.

Vertebral Fracture

Inactivity may lead to increased bone and muscle loss. Adequate pain control and early mobilization is the key to success. A brief period of partial bed rest (4 days or less, including a few 30 to 60 minute periods each day of sitting upright and walking) and bracing may be helpful for acute symptomatic cases. Prolonged bed rest and long-term use of bracing should be discouraged.

Specific exercises can promote spinal extension strength, strength around the shoulder blades, flexibility, balance and posture. It is important to educate the patient to avoid vigorous spinal movements, especially with forward bending and twisting in the upright position (spine loaded). Maintenance of spinal range in flexion and rotation is important, and these movements should be done in the lying position (spine unloaded).

CONCLUSION

In the light of recently published data, updated guideline recommendations have been produced for the assessment and treatment of osteoporosis in clinical practice. A simplified algorithm is enclosed in Fig. 2 for reference. As local data on cost-benefit profile of individual therapeutic agents is lacking, treatment of individual subjects should be assessed carefully as many of these patients will be elderly and life expectancy and coexisting medical conditions must be considered when recommending treatment. More local researches are needed for cost-effectiveness of various treatment modalities as well as a common DXA diagnostic cut-off value for our local population.

REFERENCES

1. The Working Group for Formulating Clinical Management Guidelines for Osteoporosis in Hong Kong. Clinical management guidelines for osteoporosis in Hong Kong. Hong Kong Med J 1998;4(4):423-31.
2. Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24-35.
3. Torgerson D, Cooper C. Osteoporosis as a candidate for disease management: Epidemiological and cost of illness considerations. Dis Management Health Outcomes 1998;3:207-14.
4. Randell A, Sambrook PN, Nguyen TV, et al. Direct clinical and welfare costs of osteoporotic fractures in elderly men and women. Osteoporos Int 1995;5:427-32.
5. Lau EMC, Suriwongpaisal P, Lee JK, Das De S, Festin MR, Saw SM, Khir A, Torralba A, Sham A, Sambrook P. Risk factors for hip fracture in Asian men and women – the Asian Osteoporosis Study (AOS). J Bone Miner Res 2000;16(3):572-80.
6. Lau EMC, Woo J, Leung PC, Leung D. Low bone mineral density, grip strength and skin-fold thickness are important risk factors for hip fracture in Hong Kong Chinese. Osteoporos Int 1993;3(2):66-70.
7. Lau EM, Cooper C, Wickham C, Donnan S, Barker DJ. Hip fracture in Hong Kong and Britain. Int J Epidemiol 1990 Dec;19(4):1119-21.
8. Villa ML, Nelson L. Race, Ethnicity, and Osteoporosis. In: Marcus R, Feldman D, Kelsey J (eds) Osteoporosis. California: Academic Press, 1996, pp 435-47.
9. Lau EM, Cooper C, Fung H, Lam D, Tsang KK. Hip fracture in Hong Kong over the last decade - a comparison with the UK. J Public Health Med. 1999 Sep;21(3):249-50.
10. Lau EMC, Lee JK, Suriwongpaisal P, et al. The incidence of hip fracture in five Asian countries – the Asian Osteoporosis Study (AOS). Osteoporos Int 2001;12:239-43.

11. Xu L, Lu A, Zhao X, Chen X, Cummings SR. Very low rates of hip fracture in Beijing, People's Republic of China, the Beijing Osteoporosis Project. Am J Epidemiol. 1996;144(9):901-7.
12. Cooper C, Campion G, Melton LJ III. Hip fractures in the elderly: A worldwide projection. Osteoporos Int 1992;2:285-9.
13. Ettinger B, Black DM, Nevitt MC, et al and The Study of Osteoporotic Fractures Research Group. Contribution of vertebral deformities to chronic back pain and disability. J Bone Miner Res 1992;7:449-56.
14. Melton LJ III, Lane AW, Cooper C, Eastell R, O'Fallon WM, Rigs B. Prevalence and incidence of vertebral deformities. Osteoporos Int 1993;3:113-9.
15. Jones G, White C, Nguyen T, Sambrook PN, Kelly PJ, Eisman JA. Prevalent vertebral deformities: Relationship to bone mineral density and spinal osteophytosis in elderly men and women. Osteoporos Int 1996;6:233-9.
16. O'Neill TW, Felsenberg D, Varlow J, et al and The European Vertebral Osteoporosis Study Group. The prevalence of vertebral deformity in European men and women: The European Vertebral Osteoporosis Study. J Bone Miner Res 1996;11:1010-8.
17. Ross PD, Fujiwara S, Huang C, et al. Vertebral fracture prevalence in women in Hiroshima compared to Caucasians or Japanese in the U.S. Int J Epidemiol 1995;24:1171-7.
18. Lau EMC, Chan HHL, Woo J, Black D, Nevitt M, Leung PC. Normal ranges for vertebral height ratios and prevalence of vertebral fracture in Hong Kong Chinese: A comparison with American Caucasians. J Bone Miner Res 1996;11:1364-8.
19. Lau EMC, Woo J, Chan H, et al. The health consequences of vertebral deformity in elderly Chinese men and women. Calcif Tissue Int 1998;63:1-4.
20. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporos Int 2000;11:192-202.

21. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002; 359:1929-36.
22. Position statement on the reporting of dual energy x-ray absorptiometry (DXA) bone mineral density scans. National Osteoporosis Society. 2002 Aug.
23. Kanis JA, Melton III L, Christansen C, Johnston Jr CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;8:1137-71.
24. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312: 1254-9.
25. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8:468–89.
26. Position statement on the use of quantitative ultrasound in the management of osteoporosis. National Osteoporosis Society. 2001 Dec.
27. Nelson H, Morris C, Kraemer D, Mahon S, Camey D, Nyugren P. Osteoporosis in postmenopausal women: diagnosis and monitoring. Portland: Oregon Health & Science University Evidence-based Practice Centre; 2001.
28. Kung AWC, Luk KDK, Chu LW, Tang GWK. Quantitative ultrasound and symptomatic vertebral fracture risk in Chinese women. Osteoporos Int 1999;10:456-61.
29. Ross PD, Genant HK, Davis JW Miller PD, Wasnich RD. Predicting vertebral fracture incidence from prevalent fractures and bone density among non-black, osteoporotic women. Osteoporos Int 1993;3(3):120-6.
30. Baillie SP, Davison CE, Johnson FJ, Francis RM. Pathogenesis of vertebral crush fractures in men. Age Ageing 1992;21:139-41.
31. Orwoll ES. Osteoporosis in men. Endocr Rev 1995;16:87-116.
32. Hui Y. Osteoporosis: should there be a screening programme in Hong Kong? Hong Kong Med J 2002;8(4):270-7.
33. Koh LK, Sedrine WB, Torralba TP, et al. Osteoporosis Self-Assessment Tool for Asians

(OSTA) Research Group. A simple tool to identify Asian women at increased risk of osteoporosis. Osteoporos Int 2001;12(8):699-705.

34. Kung AWC, Ho AYY, Sedrine WB, Reginster JY, Ross PD. Comparison of a simple clinical risk index and quantitative bone ultrasound for identifying women at increased risk of osteoporosis. Osteoporos Int 2003;14(9):716-21.
35. American College of Rheumatology Ad Hoc Committee on Glucocorticoid- Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoids-induced osteoporosis. Arthritis Rheum 2001;44(7):1496-503.
36. Pun KK, Chan LWL, Chung V. The problem of calcium deficiency in Hong Kong. HK Practitioner 1989;11(6):287-94.
37. Haines CJ, Chung TKH, Leung PC, Leung HY, Wong MY, Lam LL. Dietary calcium intake in postmenopausal Chinese women. Eur J Clin Nutr 1994;48(8):591-4.
38. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Effect of calcium supplementation on bone loss in postmenopausal women. N Engl J Med 1993;328(7):460-4.
39. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int. 1994;4(5):245-52.
40. Malabanan A, Veronikis IE Holick MF. Redefining vitamin D insufficiency. Lancet 1998(9105);351:805-6.
41. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly woman. BMJ 1994;308 (6936):1081-2.
42. Lau EMC, Woo J, Leung PC, Swaminathan R, Leung D. The effects of calcium supplementation and exercise on bone density in elderly Chinese women. Osteoporos Int 1992;2:168-73.

43. Kelley GA, Kelley KS, Tran ZV. Resistance training and bone mineral density in women: a meta-analysis of controlled clinical trials. Am J Phys Med Rehabil 2001;80:65-77.
44. Wang C, Collet JP, Lau J. The effect of Tai Chi on health outcomes in patients with chronic conditions: a systematic review. Arch Intern Med 2004; 8;164(5):493-501.
45. Mei J, Yeung SSC, Kung AWC. High dietary phytoestrogen intake is associated with higher bone mineral density in postmenopausal but not premenopausal women. J Clin Endocrinol Metab 2001;86:5217-21.
46. Chen YM, Ho SC, Lam SS, Ho SS, Woo JL. Soy isoflavones have a favorable effect on bone loss in Chinese postmenopausal women with lower bone mass: a double-blind, randomized, controlled trial. J Clin Endocrinol Metab. 2003;88(10):4740-7.
47. Ho SC, Woo J, Lam S, Chen Y, Sham A, Lau J. Soy protein consumption and bone mass in early postmenopausal Chinese women. Osteoporos Int 2003;14(10):835-42.
48. Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone Multicenter European Fracture Study. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. JAMA 2001;285(11):1482-8.
49. Ho KS, Chan WM. Falls in elderly – a “clinical syndrome” and a public health issue. Public Health Epidemiol Bul 2003;12(2)13-7.
50. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA 2004;291(16): 1999-2006.
51. Van Schoor NM, Deville WL, Bouter LM, Lips P. Acceptance and compliance with external hip protectors: a systematic review of the literature. Osteoporos Int 2002;13(12): 917-24.
52. Woo J, Sum C, Yiu HH, Ip K, Chung L, Ho L. Efficacy of a specially designed hip protector for hip fracture prevention and compliance with use in elderly Hong Kong Chinese. Clin Rehabil, 2003;17(2):203-5.
53. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and

cost-effectiveness analysis. Executive summary. Osteoporos Int 1998;8(Suppl 4):S3-6.

54. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spinal fractures in elderly woman. J Bone Miner Res 1996;11(12):1961-6.

55. Riggs BL, O'Fallon WM, Muhus J, O'Connor MK, Kumar R, Melton LJ III. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly woman. J Bone Miner Res 1998;13(2):168-74.

56. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337(10):670-6.

57. Papadimitropoulos E, Wells G, Shea B, et al, Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23(4):560-9.

58. Wells G, Tugwell P, Shea B, et al. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in post-menopausal women. Endocr Rev 2002; 23(4):529-39.

59. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002; 288:321-33.

60. Cauley JA, Robbins J, Chen Z, et al and Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290(13):1729-38.

61. NIH Asks Participants in Women's Health Initiative Estrogen-Alone Study to Stop Study Pills, Begin Follow-up Phase. NIH News. 2 March 2004.

62. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med. 1995;333:1437-43.

63. Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.
64. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, et al. Effect of alendronate on risk of fracture in women with low bone mineral density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.
65. Kung AWC, Yeung SS, Chu LW. The efficacy and tolerability of alendronate in postmenopausal osteoporotic Chinese women: a randomized placebo-controlled study. Calcif Tissue Int 2000;67(4):286-90.
66. Lau EM, Woo J, Chan YH, Griffith J. Alendronate prevents bone loss in Chinese women with osteoporosis. Bone 2000;27(5):677-80.
67. Cranney A, Wells G, Willan A, et al. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002; 23(4):508-16.
68. Bone HG, Hosking D, Devogelaer JP, et al and Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350(12):1189-99.
69. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604-10.
70. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 2003;349(13):1216-26.
71. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998; 339(5):292-9.
72. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging 2000;12:1-12.

73. Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23(4):517-23.

74. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282:1344-52.

75. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001;344:333-40.

76. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial; European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res 2000;15: 1006-13.

77. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997;337:1641-7.

78. Kung AWC, Chao HT, Huang KE, et al. Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women. J Clin Endocrinol Metab 2003;88(7): 3130-6.

79. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA 1999;282:637-45.

80. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial; Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281:2189-97.

81. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial.

Breast Cancer Res Treat 2001;65(2):125-34.

82. Pun KK, Chan LW. Analgesic effect of intranasal salmon calcitonin in the treatment of osteoporotic vertebral fractures. Clin Ther 1989;11(2):205-9.
83. Chesnut CH III, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109(4):267-76.
84. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in post-menopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
85. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest 1998;102(8):1627-33.
86. Reginster JY, Deroisy R, Jupsin I. Strontium ranelate: a new paradigm in the treatment of osteoporosis. Drugs Today 2003;39(2):89-101.
87. Meunier PJ, Reginster JY. Design and methodology of the phase 3 trials for the clinical development of strontium ranelate. Osteoporos Int 2003;14 (Suppl3):S66-76.
88. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350(5):459-68.
89. Chan FKW, Kong APS, Tiu SC. Increase in bone mineral density during testosterone therapy in hypogonadal men. Hong Kong Med J 2001(suppl 2); 7(4):O41.
90. Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85(8):2670-7.
91. Pearce KA, Furberg CD, Psaty BM, Kirk J. Cost-minimization and the number needed to treat in uncomplicated hypertension. Am J Hypertens 1998;11(5): 618-29

92. Rembold CM. Number-needed-to-treat analysis of the prevention of myocardial infarction and death by anti-dyslipidemic therapy. J Fam Pract 1996;42(6): 577-86.

93. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev 2002; 23(4): 570-8.

94. Ettinger B, Pressman A, Schein J, Chan C, Silver P, Connolly N. Alendronate use among 812 women: prevalence of gastrointestinal complaints, noncompliance with patient instructions, and discontinuation. J Manag Care Pharm 1998;18:1051-6.

95. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2004;89(3):1117-23.

96. Bonnick SL. Current controversies in bone densitometry. Curr Opin Rheumatol 2002;14(4):416-20.

97. Hochberg MC, Ross PD, Black D, et al. Larger increases in bone density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Arthritis Rheum 1999;42(6):1246-54.

98. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab 2002; 87(4):1586-92.

99. Miller PD, Zapalowski C, Kulak CA, Bilezikian JP. Bone densitometry: the best way to detect osteoporosis and to monitor therapy. J Clin Endocrinol Metab 1999;84(6): 1867-71.

100. Patel R, Blake GM, Rymer J, Fogelman I. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. Osteoporos Int 2000;

11:68-75.

101. Management of Osteoporosis. A National Clinical Guideline. In: Scottish Intercollegiate Guidelines Network. Jun 2003; pp11.
102. Kotal S, Ravaud P, Fechtenbaum J, Dougados M, Roux C. Follow-up of individual patients on two DXA scanners of the same manufacturer. Osteoporos Int 2000;11(8): 709-13.
103. Crandall C. The role of serial bone mineral density testing for osteoporosis. J Womens Health Gend Based Med 2001;10(9):887-95.
104. Riggs BL, Melton LJ III. Bone turnover matters: the raloxifene treatment paradox of dramatic decreases in vertebral fractures without commensurate increases in bone density. J Bone Miner Res 2002;17:11-4.
105. Rosenthall L, Caminis J, Tenehouse A. Calcaneal ultrasonometry: response to treatment in comparison with dual x-ray absorptiometry measurements of the lumbar spine and femur. Calcif Tissue Int 1999;64:200-4.
106. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J; Committee of Scientific Advisors of the International Osteoporosis Foundation. The use of biochemical markers of bone turnover in osteoporosis. Osteoporos Int 2000;11(Suppl 6):S2-17.
107. Garneo P. Markers of bone turnover for the prediction of fracture risk. Osteoporos Int 2000;11:S55-65.
108. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 2003;18(1):9-17.
109. Looker AC, Bauer DC, Chesnut CH III, et al. Clinical use of biochemical markers of bone remodeling: current status and future directions. Osteoporos Int 2000;11(6):467-80.
110. Kallmes DF, Jensen ME. Percutaneous vertebroplasty. Radiology. 2003; 229(1):27-36.

Table 1. Age-adjusted rate* of hip fracture per 100,000 population for females and males, by ethnic group and year of study

Ethnic Group	Site	Year of Study	Female	Male	Female:Male
Blacks	California, USA	1983-1984	241	153	1.6
Hispanics	California, USA	1983-1984	219	97	2.3
Asians	Hong Kong	1985	389	196	2.0
	Hong Kong	1965-1967	179	113	1.6
	Tottori, Japan	1986-1987	227	79	2.9
	Singapore	1955-1962	83	111	0.7
Caucasian	Sweden	1972-1981	730	581	1.3
	Oxford, England	1983	603	114	5.3
	California, USA	1983-1984	617	215	2.9

* Rates were age- and gender-adjusted to the 1990 US non-Hispanic Caucasian population.

Source: Villa ML, Nelson L. Race, ethnicity and osteoporosis. In Marcus R, Feldman D, Kelsey J. (eds.) Osteoporosis. Academic Press. Boston 1996.

Table 2. Age-specific incidence rates for hip fracture in Hong Kong (per 100,000 population)

Age group	Men			Women		
	1966	1985	1995	1966	1985	1995
50-59	16	28	22	22	32	26
60-69	67	54	71	54	135	108
70-79	224	339	308	173	501	581
80+	321	1156	1076	716	1521	2129

Table 3. The World Health Organization criteria for osteoporosis[23]

Diagnostic Category	Definitions
Normal	Bone mineral density (BMD) within 1 standard deviation (SD) of the young adult mean (T-score ≥-1.0)
Osteopenia	BMD more than 1 SD below the young adult mean but less than 2.5 SD below this value (T-score <-1.0 and >-2.5)
Osteoporosis	BMD being 2.5 SD or more below the young adult mean (T-score ≤-2.5)
Severe (established) osteoporosis	BMD being 2.5 SD or more below the young adult mean (T-score ≤-2.5) in the presence of one or more fragility fractures

Table 4. Secondary Causes for Osteoporosis

Medications
Steroid (especially >3 months and high doses)
Anti-convulsants (phenytoin, phenobarbital)
Excessive thyroxine
Anti-coagulant (heparin)
Immunosuppressive (e.g. cyclosporine)
Endocrine disorders
Hypogonadism
Cushing's syndrome
Hyperthyroidism
Hyperparathyroidism
Hyperprolactinaemia
Disorders of calcium balance
Hypercalciuria
Vitamin D deficiency
Gastrointestinal disorders
Chronic liver disease (e.g. primary biliary cirrhosis)
Gastrectomy
Malabsorption syndrome
Other medical diseases
Multiple myeloma
Rheumatoid arthritis
Chronic renal diseases
Lymphoma
Alcoholism
Nutritional disorder (e.g. anorexia nervosa)

Table 5. Clinical risk factors for osteoporosis

MAJOR RISK FACTORS	OTHER RISK FACTORS
History of fragility fracture Loss of height (>2cm compared to height at age 25)	Female sex Age >65 years Low body weight (<45 kg) Family history of osteoporosis or fragility fracture Premature menopause (before age of 40) or early menopause (age 40-45) Low calcium intake (e.g. lactose intolerance) Lack of exercise or sedentary life-style Smoking Excessive alcohol intake (more than four standard drinks per day) Prolonged immobilisation

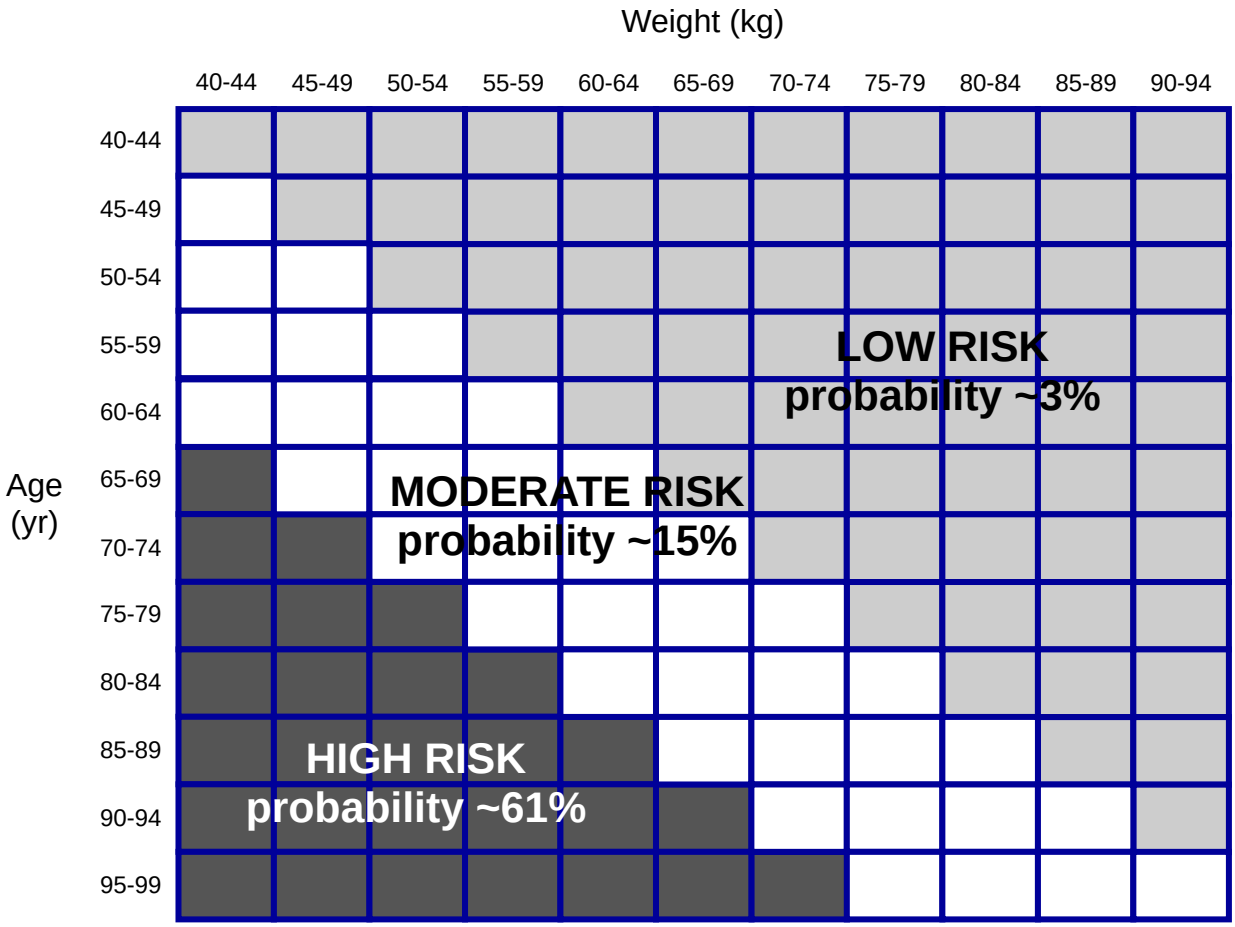
Table 6. Calcium content of some common food

Cheese	675mg/100g
Sardine	400mg/100g
Bean curd sheet	330mg/100g
Almond	250mg/100g
Yogurt	170mg/100g
Tofu	150mg /100g
Milk	120mg/100g
Broccoli	75mg/100g

Table 7. Recommended actions based on osteoporosis risk by The Osteoporosis Self-assessment Tool for Asians (OSTA)

Osteoporosis risk	**Recommended actions**
High risk	Measure BMD
Moderate risk	Measure BMD if other risk factors are present
Low risk	BMD measurement probably not necessary unless significant risk factors are present

Fig. 1 The Osteoporosis Self-assessment Tool for Asians (OSTA)



Source: Reginster JY, Kung A, Koh L, Radican L,Ross PD. A simple chart for evaluating risk of osteoporosis in Asian women based on the osteoporosis self-assessment tool for Asians (OSTA). Osteoporosis Int 13(Suppl 3):S30, 2002.

Fig. 2. Algorithm for the management of osteoporosis