OSTEOPOROSIS

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Definition of Osteoporosis

OSTEOPOROSIS is a systemic bone disease characterized by decreased bone mass density and micro-architectural degeneration, resulting in the increase of skeletal fragility and therefore the risk of fracture.

Osteoporosis is defined either by the presence of a fragility fracture or a bone mineral density (BMD) measurement which falls below a threshold level set at 2.5 S.D., below the mean peak bone mass of young adults.

Epidemiology of Osteoporosis

Thus far there are no studies conducted in Singapore to define the incidence and prevalence of the disease. However, we can extrapolate data from other countries which estimated that the proportion of women with osteoporosis increases from 15% in those aged 60 to 64 years, up to 71% in those over 80 years of age. The incidence is much lower in men, ranging from 1.6% of those aged 60 to 64 years, up to 19% of those aged over 80 years. Osteoporosis is likely to increase as the population of Singapore is aging rapidly. In 1990 only 6% of the population was above the age of 65. In 2030, this will rise to 17%.

Based on the population census statistics of Singapore in 1990, it can therefore be estimated that about 42000 females aged more than 60 have osteoporosis.

In some countries, the risk of having an osteoporotic fracture after the age of 60 years is about 60% in women and 30% in men. In Singapore, as in the rest of Asia, osteoporosis will become an increasingly important public health problem. Osteoporotic fractures at the hip, wrist and spine are increasingly common. In Singaporean men and women above the age of 50 years, hip fracture incidence rates have risen 1.5-fold and 5-fold respectively since the 1960s. Our age-adjusted rates among women over the age of 50 years are currently among the highest in Asia, and approaching those of the West. The rise in hip fracture incidence is consistent with trends seen in many other countries.

An analysis of patients who have sustained osteoporotic hip fractures in Singapore has demonstrated a mortality rate of 26% in the first year. Of the survivors, 9% were bedridden and 24% wheelchair bound.

Aetiology of Osteoporosis

The strength of the bone in later life depends on two factors – the peak strength of bone achieved in early adulthood and subsequent age-related and hormone deficiency-related bone loss

At menopause, bone turnover increases. In women, bone loss occurs by thinning, perforation and loss of connectivity. In men, there is no midlife acceleration of bone turnover.

A variety of other medical conditions, either by themselves or in relation to therapy, can lead to further and accelerated bone loss (secondary osteoporosis). A particular example of this is corticosteroids induced osteoporosis.

Diagnosis of Osteoporosis

Clinically, osteoporosis is usually defined in relation to bone density. There is a continuous inverse relationship between bone density and the risk of fracture, comparable to that between serum cholesterol and the risk of coronary heart disease. Bone densitometry measures the average density of bone mineral within the region scanned. It is

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currently the best available measure of bone strength.

Densitometry technology has advanced to such a degree that it measures apparent bone mineral density with high accuracy and precision. It is now relatively widely available and inexpensive. Dual energy x-ray absorptiometry (DXA) can provide a rapid assessment of both whole body and regional bone mass (and calculated "area density").

Due to differences in both hardware and software, bone density values obtained from instruments produced by different manufacturers cannot be compared directly. Therefore, for the diagnosis of low bone density, the individual's absolute value derived from any given instrument must be related to the sex-specific reference range derived from the same model instrument. Similarly, for meaningful detection of change over time, serial measurements in the same individual should be performed on the same instrument.

Regional bone mass measurements can be readily performed on skeletal sites commonly involved in osteoporotic fracture (e.g., lumbar spine, forearm, proximal femur).

The most validated BMD technique and site of choice for the diagnosis of osteoporosis is dual-energy x-ray absorptiometry (DXA) measured at the hip. DXA of the spine is generally the best site to monitor response to therapy. However, in older individuals, caution is required in assessing bone mass in the lumbar spine. Where there may be a partial or complete compression fracture, vascular calcification or degenerative spinal disease, the hip measurement would be preferable for monitoring purposes. Greater diagnostic accuracy may result from bone mass measurements at more than one skeletal site. An appropriate interval for repeat evaluations is after one year.

Measurements using other techniques (e.g. ultrasound scan), or at other skeletal sites are not well correlated because of differing measurement accuracies and variability in bone composition and rates of loss, resulting in T-scores yielding different information on fracture risk compared to hip DXA. T-scores therefore cannot be used interchangeably between sites and techniques, and as techniques other than hip DXA have been less well validated, their use for the diagnosis of osteoporosis is not recommended.

These techniques would be reasonable in the absence of DXA, or if incorporated with the use of risk factors in comprehensive fracture risk assessment, to aid in directing interventions to those at high risk. However, in Singapore, DXA of the hip and spine are widely available.

There is little data on the use of other techniques in monitoring response to therapy.

The case-finding screening may be better than population screening, considering that:

i) Increasing number of patients at risk (i.e. the elderly)
ii) High cost of BMD

This involves clinically evaluating individuals for their risk of having osteoporosis, and measuring BMD in those at highest risk (Table 2). Tools such as the Osteoporosis Self-assessment Tool for Asians (OSTA) (Table 1) or National Osteoporosis Foundation (NOF) guidelines may be used for initial risk stratification. The presence of other clinical risk factors or past fractures can be used to further define individuals who are at higher risk. This subgroup of patients should have BMD measurements done.

TABLE 1: Selection of postmenopausal women using Age and Weight (modified from the OSTA)

Patient's Age (yr) minus Weight (kg)	Osteoporosis Risk	Suggested Action
> 20	High	Measure BMD
0 – 20	Moderate	Measure BMD if other risk factors are present or past history of fracture
< 0	Low	Can defer BMD unless at risk or has past history of fracture

TABLE 2 : Risk factors for osteoporosis and fracture

Risk factors for low bone mass for which BMD measurement might be considered:

Non-modifiable

- Personal history of previous fracture as an adult
- History of fracture in a first degree relative (especially maternal)
- Low body weight & increasing age (Table 1)
- Poor health / frailty
- Increasing height (> -1.6m among Asian women, > -1.7m among Asian men)

Potentially Modifiable

- Current cigarette smoking
- Alcohol abuse
- Early natural or surgical menopause before age 45 years, or prolonged premenopausal amenorrhea (> 1 year)
- Drugs e.g. corticosteroids (equivalent to prednisolone > 7.5 mg/day for more than 6 months), excess thyroxine, anticonvulsants
- Ongoing disease conditions e.g. hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, chronic obstructive airways disease, liver disease, malabsorption, chronic renal failure, rheumatoid arthritis, organ transplantation and anorexia nervosa
- Low calcium intake (< -500 mg/day among Asians)
- Low physical activity (current and between 25 – 50 years of age)

Other BMD-independent risk factors for fracture:

- One or more previous falls in the past year
- Strokes, poor balance, weak quadriceps muscle strength
- Impaired eyesight despite adequate correction
- Drugs e.g. sedatives, polypharmacy
- Environmental factors e.g. slippery floors, inadequate lighting

In addition to using risk factors in decision-making for BMD, several of the potentially modifiable risk factors are themselves causes of secondary osteoporosis. Clinical evaluation should be directed at actively excluding these secondary causes, for example a cushingnoid appearance from exogenous steroids, or stigmata of alcoholic liver disease, as well as assessing the risk for falls. Secondary causes and risk factors which are modifiable should be addressed, as there is evidence that bone loss and fracture risk may be reversed in some instances.

Other useful predictors of fracture risk

In addition to the fragility of bone, fracture risk is determined by the interaction of several other factors, including the risk of falls and other trauma, the adequacy of protective responses and the adequacy of soft tissue to absorb impact.

In making decisions about investigation and treatment, the individual's full risk profile should be taken into account. The most clinically useful of these predictors include:

Age, sex and family history

With ageing, there is a decrease in bone mineral density, muscle strength, balance and other factors that increase the risk of fracture. In older individuals, fracture risk doubles every five to ten years. Among women who have a history of fracture in close family members (maternal or paternal), the risk of osteoporotic fracture is almost doubled.

Prior fracture

The occurrence of one fracture increases the risk of further fractures. Low BMD alone does not explain this increased risk. Other factors may be involved.

Falls

Even in a simple fall, enough energy may be generated to fracture the femur. In young people, protective responses, the strength of the bone and the quantity of soft tissue generally prevent fractures from occurring. In elderly people, other factors such as increased body sway and reduced muscle strength, Parkinson's disease, poor vision, physical inactivity and psychotropic medications, may have an important influence on the risk of falling.

Low body weight

Low body weight is associated with low bone mineral density and decreased soft tissue protection, both of which are associated with increased fracture risk.

Other risk factors

There is reasonable evidence of several other risk factors for fracture: very low calcium intake, smoking, menstrual irregularity/absence and some medications, particularly corticosteroids.

Bone Turnover Markers

Biochemical indices of bone turnover have the potential of aiding in risk assessment as well as for use in the monitoring of response to treatment. There is currently no role for bone turnover markers in the diagnosis of osteoporosis.

Management of Osteoporosis

Risk of osteoporosis can be decreased by maintaining adequate calcium intake, regular exercise, cessation of smoking and avoiding excessive alcohol consumption. Modifying the environment to reduce the risk of falling is important in preventing fractures resulting from osteoporosis.

Patients with established osteoporosis should be considered for treatment with drugs shown to reduce the risk of fractures. The decision to treat and choice of therapy would depend on fracture risk, the relative anti-fracture efficacy of available drugs. Other drug factors such as non-skeletal benefits, contraindications, side effects, cost and convenience must also be considered.

Patients without fracture but with osteopenia may be considered for treatment, but to date, no drug has been shown to reduce the risk of fracture in this group of patients.

Special instances of osteoporosis, such as in premenopausal women, men and in patients on corticosteroids, may require assessment and management at specialist osteoporosis clinics.

General advice

In adults, trials using weight training or increasing calcium intake by about 1000 mg/day have achieved differences of 1%-3% in bone mass over two years. These effects are small in relation to the 5%-10% differential in mass, theoretically needed to alter fracture rates by 25%-50%. Whether these results are due to changes in bone mass homeostasis or whether they reflect a continuing effect on loss of bone is unclear.

The effects of exercise on fall reduction may be more important than any other effects on bone density.

Specific therapies

Decisions about management depend on the absolute risk of fracture and the potential benefits and adverse effects of alternative treatment options. For those at moderate risk, prophylaxis or intervention should have minimal adverse effects. For those at high risk (e.g., previous fracture, very low bone density), more aggressive therapy is indicated.

Although most fracture studies have been performed on women, the relationship between bone density and fracture is similar in men. Therefore, treatments which increase bone density in women, are likely to have equivalent efficacy in men. With all therapies for osteoporosis, it is likely that the beneficial effects of fracture risk are maintained only for a limited period after the treatment is stopped.

Hormone replacement therapy

Hormone replacement therapy has been shown to prevent early postmenopausal bone loss. Long-term therapy (for more than five to ten years) after menopause probably reduces fracture risks, although it may need to be continued indefinitely to show any benefit. In late postmenopausal women, hormone replacement therapy may increase bone density by about 5% above baseline in the lumbar spine over two years. Observational studies have shown its use to be associated with reduced fracture rates throughout the skeleton, and vertebral fractures have been shown to be reduced in randomised controlled trials. There is no data from randomised controlled trials on the effects of hormone replacement therapy on hip fractures. Hormone replacement therapy has other benefits in postmenopausal women. It relieves urogenital symptoms and may be associated with a reduction in the incidence of cardiovascular disease. It is clear that any effects on the risk of breast cancer is small; evidence of the risk from long-term use (more than five to ten years) is still pending from current prospective randomised studies. The effects on bone density of oestrogen with supplemental calcium may be additive or more than additive.

The extensive documentation on its efficacy and safety makes hormone replacement therapy the

treatment of choice in postmenopausal osteoporosis.

Bisphosphonates

The early bisphosphonate, etidronate, increases bone density in the lumbar spine by 3%-5% above baseline after two years of therapy in late postmenopausal women, with a reduction in fracture risk. Newer, more potent bisphosphonates may have a better therapeutic profile. Two of these, alendronate and residronate, found increases in bone density comparable to those seen with hormone replacement therapy, and a reduction in relative fracture risk of about 50%. There is little experience with bisphosphonate use beyond five years of continuous therapy. Their safety and efficacy make the newer, more potent bisphosphonates first line therapy in older individuals unable or unwilling to take hormone replacement therapy.

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) which prevents bone loss and reduces vertebral fracture risk, but not non-vertebral fracture risk. Raloxifene appears to decrease the risk of breast cancer, but is associated with an increased risk of thromboembolism.

Vitamin D (calciferol)

Recent studies from a number of countries have demonstrated that Vitamin D deficiency is common in the institutionalised elderly due to poor sunlight exposure. Correction of this deficiency reduces hip and other non-vertebral fractures. This intervention involves the use of replacement doses of calciferol (500-1000 units/day or 50 000 units/month). Avoiding Vitamin D deficiency in this at-risk group is an important part of providing care for the elderly. The continuing availability of oral formulations of Vitamin D is a priority (supplies of vitamin D were difficult to obtain last year, despite being listed on the PBS).

Active vitamin D metabolites (calcitriol)

Calcitriol has a therapeutic profile distinct from Vitamin D and should not be used in the treatment of Vitamin D deficiency. Calcium supplements should be stopped while using calcitriol.

There are disagreements about the place of active Vitamin D metabolites in the management of postmenopausal osteoporosis. One study showed a reduced fracture rate with calcitriol, while other smaller studies with limited power did not. Calcitriol may be more effective in people with reduced efficiency of calcium absorption. These uncertainties should be resolved by further large randomised controlled trials. However, calcitriol may play a major role in the management of glucocorticoid-induced osteoporosis. In patients commencing glucocorticoid, calcitriol has been shown to prevent spinal bone loss.

Calcium

Long-term high calcium intake in postmenopausal women appears to prevent or reduce loss of bone, resulting in a 1%-3% difference in bone density compared with untreated individuals over two years. Several small studies in the elderly have suggested there may also be a reduction in the number of fractures after taking calcium supplementation. Although calcium intake by itself is less effective than hormone replacement therapy or other therapies, adequate calcium intake should be part of routine management. The target total intake should be about 1500 mg/day in those not using more effective treatments. Dietary and supplemental forms of calcium appear to be equally well absorbed, with no need for additional

components for effective absorption other than normal Vitamin D status.

Other agents

Anabolic steroids (e.g., nandrolone decanoate) are testosterone analogues. A number of randomised controlled trials have shown moderate increases in spinal bone mineral density. However, data regarding their anti-fracture efficacy are inconclusive. Their long-term use in effective doses is accompanied by a high incidence of side effects. The use of fluoride should be restricted to research and specialist centres.

Calcitonin is an antiresorptive agent used in some parts of the world for treating osteoporosis. Its expense, side effects and difficulties with administration mean that it is not widely used in most countries.

Hip protectors have been shown in one randomised controlled study to halve the rate of fractures in the institutionalised elderly, although compliance may be poor.

Alternative therapies

In the community, a variety of alternative therapies, such as phytoestrogens, herbal medicines and nutritional additives, are used for osteoporosis. Their effectiveness for prevention of osteoporotic fractures have not been proven in scientific studies. In addition, their cost and potential side effects must be considered.

Treatment Objectives

THE KEY OBJECTIVES in managing osteoporosis are to:

- Restore and maintain bone strength to prevent fractures; and
- Reduce the overall morbidity and mortality associated with the condition.

Encouraging adequate calcium and Vitamin D intakes and modification of other lifestyle factors such as smoking, excessive alcohol intake, inactive lifestyle or excessive exercise is appropriate in all individuals, from childhood to old age.

THE GOAL in treating osteoporosis is to prevent fractures. However, fractures are not sufficiently frequent events in individuals to meaningfully reflect the adequacy of therapy, so bone density is an important surrogate endpoint.

Fall Prevention

Falls prevention programs are worth considering in the reduction of future fractures.

Multifactorial falls prevention strategies have been shown to be effective in some studies. These include specific exercise programs, medication management (especially to reduce the use of sedatives and tranquillisers), assessment of vision and footwear, and home and environmental modifications.

Analysis of data from studies have found that quadriceps strength, postural sway and bone density were independent predictors of subsequent fracture. Most observational and epidemiological studies suggest that physical activity is associated with a reduced risk of falling, likely because of improved balance and coordination skills.

Hip protectors reduce the incidence of hip fractures, especially in nursing home residents. More research is needed on their effectiveness and particularly on their acceptability.

Falls prevention programs are likely to be most effective when aimed at "at risk" individuals in the community. However, they are not necessarily inexpensive and more research is required to identify the components (e.g., balance training) which are most effective and cost-effective.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels Ic, IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

TABLE 3 – Efficacy of population-based preventive approaches

Intervention	BMD	Vertebral fracture reduction	Hip fracture reduction
Dietary calcium	B	B	B
Calcium (± vitamin D) supplements	A	A	A
Exercise	A	B	B
Smoking cessation	B	B	B
Reduced alcohol intake	C	C	B
Fall prevention	-	-	-
Hip protectors	-	-	A

TABLE 4 – Grades of Recommendations for Therapeutic Interventions

Drug	Benefit in BMD	Vertebral fracture reduction	Non-vertebral fracture reduction	Hip fracture reduction
Calcium & vitamin D	A	A	A	A
HRT	A	A	A	B
Alendronate	A	A	A	A
Risedronate	A	A	A	A
Etidronate	A	A	B	B
Clodronate	A	-	-	-
Raloxifene	A	A	-	-
Calcitonin	A	A	B	B
Calcitriol	A*	A*	A	-
Alfacalcidol	A	A	-	-
Anabolic steroids	A	-	-	B
Ipriflavone	A*	-	-	-
Parathyroid hormone	A	A	A	-
Fluoride	A	A*	-	-
Combination therapy	A	-	-	-