

Clinical Update on Osteoporosis

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Abstract

Osteoporosis and fractures are an increasing problem in many countries. Continued research into the genetics and molecular pathophysiology of osteoporosis improve our understanding of this disease, and may provide insights into novel strategies or therapeutics which might be developed. Increased awareness of the epidemiology of osteoporosis, risk factors, and the availability of methods to quantify skeletal integrity such as bone densitometry, allow the condition to be anticipated and diagnosed before fractures occur, and facilitate measured decisions about further evaluation and appropriate management. As with most chronic diseases, healthy lifestyle measures are recommended. In addition, pharmaceutical options which have been shown to be effective in reducing fracture rates among those with or without fractures are increasingly available. The decision to institute therapy and choice of drug should ideally be rational and individualised.

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Key words: *Diagnosis, Epidemiology, Fracture, Treatment*

Introduction

Fractures, the most serious complication of osteoporosis, are increasing and constitute an evolving public health problem in terms of disability, mortality and cost. A paradigm shift in the management of osteoporosis has resulted from the development of techniques which can diagnose osteoporosis before fractures occur, and effective medications which reduce the risk of first and recurrent fractures. Because of the large costs involved, developing the most efficient methods to utilise these diagnostic and therapeutic modalities is important.

Pathophysiology

Osteoporosis results as a culmination of events: failure to attain genetically programmed peak bone mass, increased loss of bone subsequently, or a combination of both, and also deficits in other determinants of bone strength.

The main determinant of peak bone mass is genetic factors. Twin and family studies have suggested that up to 80% of the variance in peak bone mass¹ and bone metabolism² is genetically determined. However, research has revealed weak associations of bone density, bone turnover and fractures with gene polymorphisms such as those of the vitamin D receptor (VDR), collagen 1 α 1 gene (COL1A1), oestrogen receptor (ER) and other candidate genes,¹ or combinations of genes.³ The distribution of these

polymorphisms differs geographically, and their impact on the skeleton appears to be variable in different populations, possibly related to the way they relate to environmental factors.¹ Non-genetic factors such as nutrition, exercise, a normal hormone milieu and social habits are other important determinants of peak bone mass.⁴

Bone loss occurs as a result of an increased rate of bone remodelling and an imbalance between the activity of osteoclasts and osteoblasts. The major causes of bone loss relate to oestrogen deficiency and ageing,⁵ where the intricate molecular interactions at the cellular level between oestrogen, androgens, parathyroid hormone, vitamin D, growth factors, including insulin-like growth factor I and transforming growth factor- β , and cytokines such as the interleukins, tumour necrosis factor, osteoprotegerin and bone morphogenic proteins, are likely to feature.⁶ Other accelerating factors such as drugs, illnesses and toxins also contribute to bone loss.

Other determinants of bone strength which contribute to increased fracture risk include bone geometry, bone fatigue, and loss of trabecular connectivity.⁷

Continued research into the genetics and molecular pathophysiology of osteoporosis improve our understanding of this disease, and may provide insights into novel strategies or therapeutics which might be developed to address this problem.

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Epidemiology

As the number and proportion of the elderly in many countries is increasing rapidly, the problem of osteoporosis will continue to increase. Increases in hip fracture rates have been documented in many countries⁸ including Singapore,⁹ and further increases in hip fracture incidence to epidemic proportions are predicted worldwide.¹⁰ Vertebral fracture rates among Asian populations are already similar to Caucasian populations.¹¹

In several large epidemiological studies, including recent studies from Asia,^{12,13} many risk factors have been found to be associated with osteoporosis,¹⁴ falls¹⁵ and fractures.^{16,17} These risk factors have been used both qualitatively and quantitatively, in the development of scoring systems to enhance case-finding strategies for the detection of osteoporosis,¹⁸ as well as in predicting shorter-term fracture risk e.g. over 5 years,¹⁹ which may affect the decision to initiate therapy.

Diagnosis

Unless the patient has suffered a previous fracture, which suggests skeletal fragility, non-specific body aches and pains should generally not be attributed to osteoporosis unless there is progressive deformity or radiological documentation of fractures.²⁰ In the absence of fractures, the description of 'radiographic osteopenia' might subjectively suggest the presence of osteoporosis, but this needs to be quantified objectively.²¹

The conceptual definition of osteoporosis as a 'progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture',²² captures the notion that bone mineral density (BMD), a measure of bone mass, is central to the diagnosis in the absence of a fracture, and that an individual experiencing a fragility fracture also has osteoporosis, regardless of bone density.

The operational definition of osteoporosis as a value for BMD that is 2.5 standard deviations (SDs) or more below the mean value in young adults ($T\text{-score} \leq -2.5 \text{ SD}$)²⁰ allows standardization of the diagnosis, and has been widely used in epidemiological and clinical intervention trials, and in clinical practice.

In recent years, several techniques have been available for the measurement of BMD, but the technique of choice remains dual-energy X-ray absorptiometry (DXA) of the hip since this method has been the most validated against fracture risk.^{21,23} T-scores from the different techniques are not interchangeable, limiting the usefulness of other techniques in the diagnosis of osteoporosis. Heterogeneity also exists between skeletal sites in that low BMD at one site does not necessarily confirm low BMD at another.²⁴

The lumbar spine is the preferred site for monitoring therapeutic response since in most trials, the largest changes in BMD in response to treatment have occurred at the lumbar spine.²⁵⁻³⁵ However, where spurious increases in BMD may occur, particularly in the elderly, monitoring is best done at the hip site. There is limited data on the use of peripheral techniques in monitoring response to therapy because the overwhelming majority of intervention trials in osteoporosis utilised DXA to measure BMD.²⁵⁻³⁵ Because absolute BMD values differ between Asian and Caucasian populations,³⁶ Asian reference databases, if not ethnic group-specific databases, should be used for deriving local T-scores.

There is some controversy with regard to the diagnostic threshold for osteoporosis in men,^{37,38} but the BMD value in men which corresponds to the female femoral neck T-score of 2.5 SD or more below the reference range for young women has been recommended as the male threshold value.²³

There is no role for biochemical markers of bone turnover in the diagnosis of osteoporosis although there may be a role as a risk factor in predicting fracture risk or in monitoring response to anti-resorptive therapy.²¹

Secondary causes of osteoporosis should be considered and evaluated for, since part of the management of osteoporosis would be to reverse these causes as far as possible. Patients should not be treated with drugs for osteoporosis unless a definitive diagnosis of osteoporosis is made.

Management

Healthy lifestyle recommendations including adequate dietary calcium and vitamin D intake, exercise, the cessation of smoking and avoidance of alcohol abuse continue to be encouraged, and strategies to reduce the risk of falling or the degree of injury from falls, such as by modifying the environment, should be implemented. However, employing healthy lifestyle measures alone is insufficient if the individual has osteoporosis, since effective therapies are available.

Patients with osteopenia but without fractures may be considered for 'prevention' to maintain bone density above the osteoporotic threshold.²¹ However, it must be borne in mind that ultimately, the most important measure of the effectiveness of any therapeutic measure is anti-fracture efficacy. A recent meta-analysis on hormone replacement therapy has suggested a reduction in non-vertebral fractures particularly in early postmenopausal women.³⁹ Recent preliminary abstract data suggest that raloxifene may reduce vertebral fractures in women with osteopenia.⁴⁰ Other therapies initiated in osteopenic patients over periods of 2 to 4 years have resulted in increased BMD, but have

generally not been shown to reduce fracture risk, such as with alendronate,²⁶ cyclical etidronate,²⁷ risedronate²⁸ and intranasal calcitonin.²⁹ In general, though, osteopenic women as a group is large and usually younger. Such women have a relatively low 5-year fracture risk overall, and a different pattern of fractures from older women, with wrist and other non-major fractures occurring more frequently than vertebral fractures, and hip fractures occurring even less.⁴¹ Such women need to be cognizant of the benefits against the risks of these therapies should therapy be considered.

Patients with established osteoporosis, either with BMD T-score ≤ -2.5 SD or with fragility fractures, should be considered for treatment with drugs shown to reduce the risk of the first fracture or further fractures. The drugs with the most rigorous experimental data showing fracture reduction include the bisphosphonates, alendronate^{30,31} and risedronate,³³ raloxifene³² and intermittent parathyroid hormone therapy.³⁵ Other drugs with some evidence for anti-fracture efficacy include hormone replacement therapy,^{39,42} cyclical etidronate⁴³ and calcitonin.³⁴ The effectiveness of vitamin D analogs, such as calcitriol and alphacalcidol,⁴⁴ and fluoride,⁴⁵ remains doubtful as both reductions and increases in fractures have been demonstrated in different trials. Calcium and vitamin D remain as supplementary to other forms of treatment for osteoporosis, except in housebound individuals where calcium and vitamin D deficiency are likely.⁴⁶

Treatment of patients with baseline fragility fractures (e.g. vertebral fractures) is probably more cost-effective because incidence of subsequent fracture is higher compared to patients without fracture.³⁰⁻³² The decision to institute treatment should be guided by an integration of fracture risk, considering the patient's age, BMD, and the presence of other risk factors for fracture, falls or bone loss. The choice of therapy would depend on the relative anti-fracture efficacy of available drugs, other non-skeletal benefits, adverse effects, cost, convenience of administration, and whether the patient has contraindications to using the drug.

Conclusion

As awareness of the importance and impact of osteoporosis increases, continued research and the evolution in knowledge has allowed this problem to be addressed in many fronts. While the challenge remains to improve on the effectiveness of diagnostics and therapeutics, probably the greater challenge is to develop cost-efficient strategies to manage the majority of individuals at risk or suffering from this worldwide epidemic.

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QUESTIONS

1. Osteoporosis may be diagnosed solely on the basis of:
 - a) symptoms of backache
 - b) spine radiographs
 - c) bone ultrasound measurements of the heel
 - d) biochemical markers of bone turnover
2. The following concepts in osteoporosis are true:
 - a) A patient with a fragility fracture has osteoporosis, regardless of bone mineral density (BMD).
 - b) Osteoporosis can be diagnosed before fractures occur.
 - c) There is good evidence that treating women with bone aches and joint pains, or with risk factors for osteoporosis without measuring BMD using drugs for osteoporosis will reduce their symptoms or reduce fracture risk.
 - d) Individual gene polymorphisms are strongly linked with osteoporosis and fractures.
3. With regard to bone density measurements,
 - a) dual-energy X-ray (DXA) absorptiometry of the hip is the technique of choice to diagnose osteoporosis.
 - b) monitoring of response to treatment can reliably be assessed using forearm DXA or calcaneal ultrasound.
 - c) low BMD measured at the calcaneus confirms that low BMD will be found at the hip or spine.
 - d) although somewhat controversial, the threshold for male osteoporosis is generally accepted as <2.5 S.D. of the female peak BMD.
4. When deciding on initiating therapy for osteoporosis,
 - a) there is compelling evidence that many therapies for patients with osteopenia result in significant fracture reduction.
 - b) there is good evidence that treatment of patients with osteoporosis results in significant fracture reduction.
 - c) the most cost-effective group of osteoporotic patients to treat are those with baseline fragility fractures.
 - d) the decision to institute therapy depends not only on BMD, but ideally involves an integration of risk factors for fracture as well.
5. In choosing drug therapy for osteoporosis,
 - a) calcium supplements or an increase in dietary calcium intake is sufficient treatment for patients with osteoporosis.
 - b) the strongest evidence-based reductions in fracture risk in osteoporotic patients have been demonstrated with alendronate, risedronate, raloxifene and intermittent parathyroid hormone therapy.
 - c) there is good evidence that vitamin D analogs such as calcitriol and alphacalcidol are effective in reducing fracture risk.
 - d) apart from anti-fracture efficacy, factors which we might take into consideration in choosing the most appropriate therapy include non-skeletal benefits, cost, ease of compliance, side effects and contraindications.

ANSWER SHEET

Continuing Professional Development:
Clinical Update on Osteoporosis

Question 1

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 2

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 3

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 4

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 5

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

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