A rational approach to the treatment of osteoporosis

Hough S, MBChB, HonsBSc, MMed, MD (Stell), FCP(SA)
Professor of Medicine & Endocrinology
Faculty of Health Sciences
University of Stellenbosch

Correspondence to: Prof S Hough, e-mail: fsh@sun.ac.za

Abstract

Osteoporosis is a common, costly and serious disease. The life-time risk of an osteoporotic fracture in Caucasian women approximates 50%. Epidemiologic fracture data in South Africa are limited, but the incidence of osteoporosis appears to be similar in white, Indian and mixed ancestry (Coloured) females.

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Introduction

Hip fractures are clearly less prevalent in our Black population, but unlike African American women, the spine bone mass and fracture rate of black and white South African women appear to be comparable. In Europe and America, about 25-30% of hip fractures occur in men; in developing countries including South Africa, men account for 50% of all hip fractures. Approximately 20% of all hip fracture patients die within 1 year of the event; even more disconcerting is the fact that 50% are incapable of leading an independent life, and usually require institutionalisation. It is furthermore predicted that the prevalence of fractures will increase in future, yet no more than 10-20% of all women who sustain an osteoporotic fracture currently receive appropriate treatment for osteoporosis.

Definition of osteoporosis:

Originally defined on a histologic or clinico-radiologic basis, the diagnosis of osteoporosis has for the past decade, depended nearly entirely on the accurate measurement of bone mass (as bone mineral density, BMD) employing dual energy x-ray absorptiometry (DEXA), and its densitometric classification into normal, low BMD (osteopenia), osteoporosis (OP) and severe OP categories.

While the four diagnostic categories of this WHO classification (Table I) have provided a practical basis to identify those at risk of sustaining a fracture, we do need to take cognisance of the limitations of raising a risk factor for fracture (albeit an important one like BMD), to the status of a diagnostic criterium:

i. A single BMD measurement lacks sensitivity and up to 50% of patients with a known osteoporotic fracture may have a BMD value that is not in the osteoporosis range i.e. a BMD – the so-called T-score – which is 2.5 SD or more below the peak value in young adults.
ii. The WHO criteria are based on data obtained from white postmenopausal women employing DEXA of the axial skeleton, and cannot be extrapolated to other populations (young individuals, Blacks, males) or to other techniques that measure BMD (e.g. QCT, ultrasound). Under these circumstances, a diagnosis of OP is best considered if the so-called Z-score (BMD compared with age, gender and race-matched controls) is below -2.
iii. Causes of a low BMD other than osteoporosis (e.g. primary hyperparathyroidism, osteomalacia) are not considered
iv. Extraskeletal risk factors (e.g. propensity to falls) are not addressed.
v. Qualitative bone changes are not assessed (Table II).

Table I: WHO Criteria for Osteoporosis in Women

Normal	BMD or BMC < 1SD below the young adult reference range
Low bone mass	BMD or BMC 1 - 2.5SD below the mean of young healthy women
Osteoporosis	BMD or BMC > 2.5SD below the mean of young healthy women
Severe osteoporosis	BMD or BMC > 2.5SD below the mean of young healthy women and the presence of one or more *fragility fractures*
WHO Technical Report Series: B43,1994	

Table II: Definitions of Osteoporosis

Mass-based	Non-mass determinants
• Sensitivity	• Age
• WHO-cohort	• Genetics/ Ethnicity
• Other causes of low BMD	• Turnover
• Qualitative factors	• History of fractures
• Extraskeletal factors	• Drug trials
	• Falls

Numerous recent studies have emphasized the importance of bone quality as a major BMD - independent risk factor for fracture. Unfortunately bone quality cannot readily be measured and surrogate markers (e.g. biochemical markers of bone turnover) therefore need to be employed (vide infra).

Pathophysiology and risk factors:

Since bone mass accounts for approximately 70% of the variance in bone strength *in vitro*, and is the only variable that can be accurately determined, its measurement (as BMD) currently embodies the practical basis for the diagnosis of osteoporosis.

Bone mass is essentially a function of:

i. Peak bone mass (PBMD) attained during early adulthood.
ii. Age related bone loss
iii Total duration of loss

PBMD is largely (±70%) determined by heredity and gender, although nutrition (especially total energy and calcium intake), physical activity, pubertal development and general health may exert a considerable influence. Age-related bone loss appears to result mainly from menopausal hormone deficiency (resulting in increased bone resorption), and progressive age-related osteoblast incompetence (resulting in impaired bone formation). Additional factors are, however, clearly operative but poorly understood (e.g. all women age and become oestrogen deficient, yet not all develop osteoporosis). If ***genetic*** (both a maternal and paternal history of OP is important) or ***lifestyle factors*** (poor nutrition, lack of exercise, smoking and alcohol abuse), ***diseases*** (e.g. endocrine, malignant, gut disorders), and/or ***bone toxic drugs*** (notably glucocorticoids, but also anti-epileptic agents, anti-coagulants, HAART, immunosuppressive drugs etc) are superimposed on age-related (involutional) bone loss, significant osteoporosis may ensue (Table 3).

Table III: Risk Factors & Causes of Osteoporosis

• Genetic and ethnic factors
• Environmental factors
– Lifestyle
Diet
Exercise
Alcohol
Smoking
– Medical
Hormones
Bone Toxins
Malignant disorders
Others
• Age-related factors
– Hypogonadism
– Ageing

A number of risk factors for osteoporosis have been identified. The weighting and prioritization of such risk factors may differ from one area to another, but the following factors are usually clinically useful to identify women at risk of sustaining an osteoporotic fracture:

- A ***low BMD*** (fracture risk doubles for each SD decrease in T-score)
- Advanced ***age***
- ***Prior fragility***
- ***Fracture*** (increases fracture risk fivefold)
- A ***family history***
- ***Low body weight*** (BMI <19kg/m^2)
- ***Chronic glucocorticoid use*** (>3 months. regardless of dose)
- ***Smoking and alcohol abuse***
- High ***risk of falls*** (previous history of falls; general frailty and sarcopenia; impaired balance, gait and reduced visual acuity; drugs – e.g. sedatives, anti-hypertensives)

Diagnostic evaluation:

BMD measurement

In South Africa, with its heterogeneous populations and limited health resources, the prevention and treatment of osteoporosis is best managed employing a ***case finding*** approach, and not a ***global screening*** policy. It is suggested that clinical risk factors – related to bone mass (BMD), bone strength and/or falls – provide indications for further diagnostic assessment.

The National Osteoporosis Foundation of South Africa (NOFSA) has therefore recommended the following ***indications for BMD measurement:***

i. Diseases (endocrine, gut, malignant, nutritional/eating disorders) or drugs known to affect bone adversely
ii. Radiological evidence of vertebral deformity or osteopenia
iii. History of non-traumatic fracture after age 40 yr
iv. To facilitate the decision whether to initiate/continue HRT
v. The presence of strong historic risk factors (e.g. family history of OP, low BMI, heavy alcohol intake, smoking)

Dual energy x-ray absorptiometry (DEXA) of the axial skeleton is the preferred technique to measure BMD/ diagnose OP and to assess rates of bone loss/gain. The BMD of both spine and hip should be measured and, until local reference ranges are established, it is recommended that the NHANES III reference data be used. Since average hip and spine BMD values of black South African women and men are substantially lower than their African American counterparts, it is suggested that Causasion reference data be used in all our ethnic groups in the interim.

Radiological assessment of fracture

Standard radiology is too insensitive to be clinically useful for the early detection of bone loss – 30-40% of skeletal mass needs to be lost before loss can be reliably detected on plain radiographs. The routine radiological assessment of the spine for detection of vertebral fractures is, however, essential. More than a third of all spine fractures are asymptomatic, the patient being unaware of their presence. Yet, the presence of vertebral fracture(s) increases the risk of a subsequent fracture 4-5 fold. Moreover, vertebral fractures are also indicators of increased risk of fractures at other sites, including the hip.

Morphometric assessment of the spine to detect vertebral fracture employing standard radiology or DEXA-based imaging (LVA, IVA) should therefore comprise a routine part of the work-up of any patient with possible osteoporosis.

Biochemical markers of bone-turnover

A high bone-turnover doubles the risk of fracture, independent of BMD. Modern biochemical markers of bone resorption include urinary and serum deoxypyridinoline, as well as collagen Type I cross-linked N (NTX) and C (CTX) telopeptides, while biomarkers of bone formation include serum osteocalcin, bone specific alkaline phosphatase (BALP), and C- (PICP) and N- (PINP) propeptides of Type I collagen.

In ***population*** studies, biomarkers have been shown to be useful predictors of bone loss, fracture risk independent of BMD, and response to anti-resorptive

therapy. Technical and biological variations of up to 30% in *individual* subjects, however, limit their routine clinical use. They may be useful in problem cases (especially in the elderly) to aid in the decision whether to initiate treatment or not, and may be particularly useful to monitor therapy.

Biochemical assessment

Biochemical evaluation to exclude causes of a low BMD other than osteoporosis (primary hyperparathyroidism, osteomalacia) and to identify underlying causes of osteoporosis should be considered in all patients with proven disease. The former usually includes a serum calcium, phosphate and ALP – a serum parathyroid hormone and 25 (OH) vitamin D level may also be considered. A full blood count, ESR, protein electrophoresis and sex hormone levels in premenopausal subjects are routinely employed to identify secondary osteoporosis. Further laboratory tests are generally dictated by clinical findings.

Diagnostic criteria vs. interventional thresholds;

Although useful in epidemiologic studies and drug trials, the largely BMD-based criteria to diagnose OP lack sensitivity (>50% of subjects with an osteoporotic fracture do not have a BMD in the OP range i.e. a T score below -2.5). Similar to other chronic degenerative diseases like hypertensive stroke or dyslipidaemic coronary artery disease, ***the intervention threshold*** or need to treat cannot depend on a ***mass-based diagnosis*** only – advanced age, prior fragility fractures, strong clinical risk factors (e.g. chronic glucocorticoid use), continuing bone loss (as indicated by an increased bone turnover) are but a few non-BMD determinants of bone strength and propensity to fracture, which should be considered, in conjunction with a BMD measurement, in the rational management of this disease (See Figure I).

Non-pharmacological measures to prevent osteoporotic fractures

Non-pharmacological measures to improve bone strength include a balanced diet rich in dairy, physical exercise (weight bearing to improve bone mass, muscle strengthening to prevent falls), limiting alcohol consumption (2 units/day in both men and women; modest social drinking may have a bone protective effect in postmenopausal females), the avoidance of smoking and bone toxic drugs, and the prevention of falls (including the selective use of hip-protectors).

Pharmacologic interventions

Drugs used to treat osteoporosis are conventionally classified as antiresorptive and bone formation stimulating agents. (Table IV). These names are, however, misleading since the process of bone resorption and formation are coupled – even in most subsets of osteoporosis. So-called antiresorptive drugs therefore decrease bone resorption (within weeks), and subsequently also bone formation (within months). Likewise, bone formation stimulating drugs like teriparatide augment bone formation, which is followed by an increase in resorption a few months later.

Table IV: Drug Therapy for Osteoporosis

A. Anti-Resorptive Agents
– Calcium
– Vitamin D/Metabolites
– Sex Hormones/SERMS
– Calcitonins
– Bisphosphonates
B. Anabolic / Dual Action Agents
– Fluoride
– Anabolic Steroids
– Low - Dose Intermittent PTH
– Strontium Salts

Calcium & Vitamin D

Calcium (ensuring a daily intake of 1-1.5g) and vitamin D (800 IU/d) are routinely recommended for the prevention and treatment of osteoporosis. Their effect on BMD is, however, often modest. The ability of vitamin D (with or without calcium) to reduce vertebral fracture seems to be well documented, but effects on the rate of hip fracture remain controversial and apparently dependent, at least in part, on the study population – frail elderly subjects with a low dietary calcium intake and a low serum 25-hydroxyvitamin D appear to respond better. One of the major problems with calcium supplementation is poor compliance which can usually be ascribed to gastro-intestinal side-effects, particularly constipation.

It is important to note that sun exposure during winter in the Western Cape, results in the activation of previtamin D which is markedly less than in Gauteng. Ethnicity and religious custom (covering sun exposed surfaces) may further limit vitamin D delivery. Vitamin D supplementation is recommended for all elderly institutionalised patients. If significant deficiency is suspected, measurement of serum 25-hydroxyvitamin D is recommended. High dose vitamin D treatment (50 000 IU, 1-4 times/2weeks) should include periodic determinations of 24h urinary calcium excretion.

Active metabolites of vitamin D, calcitriol and alfacalcidiol, were shown in earlier studies to reduce the fracture rate – therapeutic and toxic doses seem to overlap and their routine use in the treatment of osteoporosis cannot be recommended.

HRT & SERMS

Data from the Women's Health Initiative (WHI) have convincingly shown that treatment of postmenopausal women with oestrogen prevents fractures of both the spine and hip. Hormone therapy is, however, not side-effect free and should probably be reserved for younger women (<60yr), especially those with menopausal symptoms.

Selective oestrogen receptor modulators (SERMS) have been shown in the MORE study to reduce the risk of spine, but not hip fracture. These agents also reduce breast cancer by 70%.

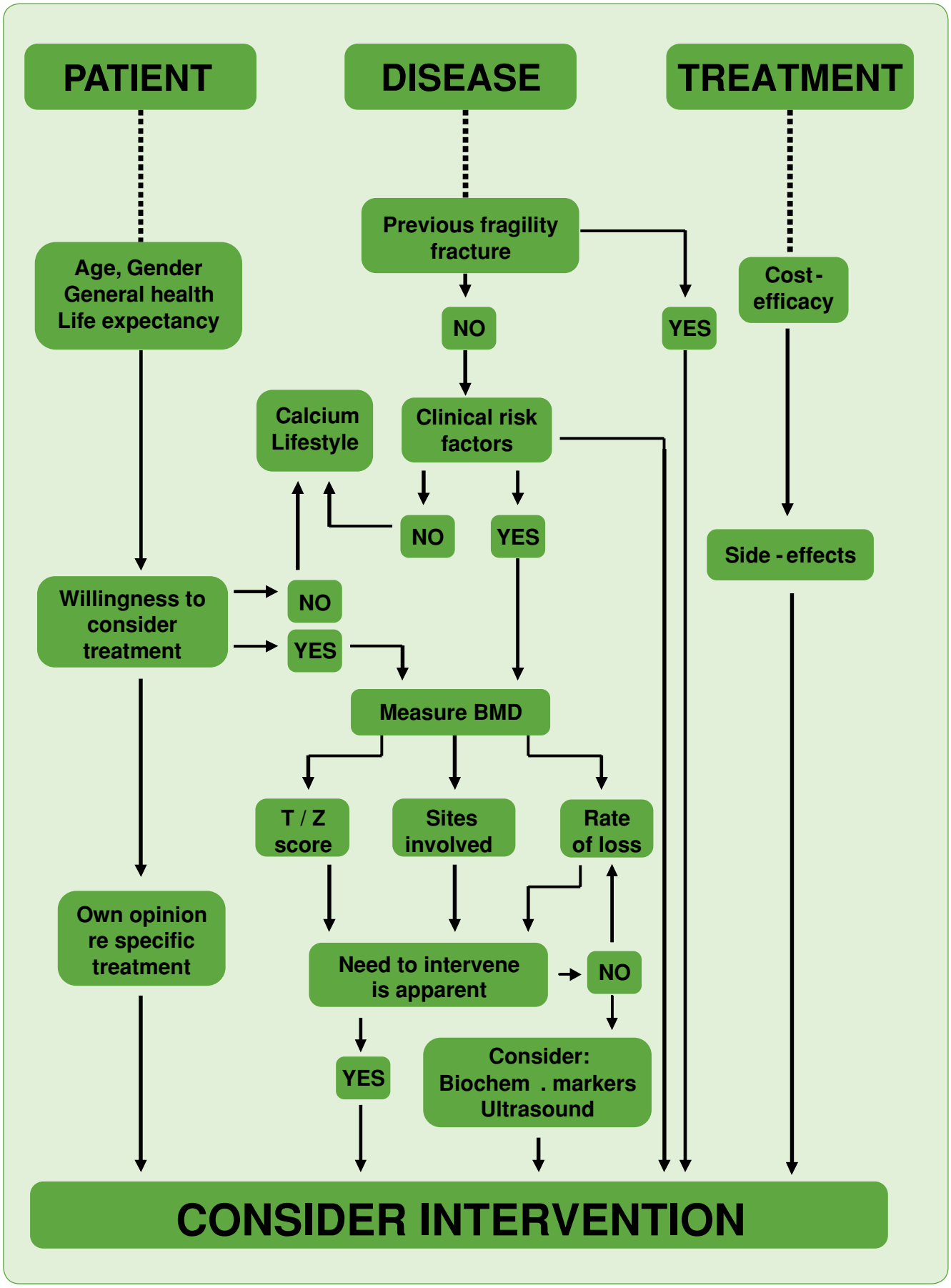
Bisphosphonates

Bisphosphonates are stable analogues of pyrophosphate which safely and effectively reduce the risk of spine and hip fractures, and remain the cornerstone of antiresorptive therapy. They do, however, have limitations related to long-term compliance, gastro-intestinal intolerance, poor absorption from the gut, and oversuppression of bone turnover (including osteonecrosis). Intermittent intravenous administration might address problems with compliance and absorption, and is the focus of much current research.

Teriparatide

Daily subcutaneous injections of human parathyroid hormone (hPTH 1-34) for as little as 21 months, markedly increase bone mass, improve skeletal micro-architecture and reduce the risk of new vertebral fractures by 65% and non-vertebral fractures by 35-40%. Given its very high cost, the National Osteoporosis Foundation (NOFSA) has recommended that this drug should only be used in patients with severe OP i.e. (i) a low BMD plus 2 or more prevalent frac-

Fig 1: Algorithm to assess whether to intervene in patients with possible osteoporosis. The intervention threshold or need to intervene should not depend on a mass-based diagnosis only, but should also take into consideration various patient, disease and treatment factors.



tures or (ii) failed antiresorptive therapy i.e. after adhering to adequate antiresorptive therapy for 12 months or more, the patient experiences: (a) an incident fracture or (b) an unacceptable rate of bone loss (e.g. a decrease in vertebral BMD of >5% per year as documented on 2 or more follow-up BMD measurements). Currently consideration is being given to extend these indications – e.g. to include glucocorticoid-induced osteoporosis.

Strontium ranelate

Strontium ranelate has a unique dual action on the skeleton – it stimulates bone formation whilst it also decreases bone resorption. This results in a marked increase in bone mass, size and strength, as well as a significant reduction in the risk of vertebral (SOTI-trial) and non-vertebral (TROPOS-trial) fractures of 41-52% and 36% respectively. In these trials, compliance with the drug was good and side-effects did not differ significantly from that of controls.

Other drugs

Calcitonin has a direct-inhibitory effect on osteoclast action and also has central opiate-mediated analgesic properties. Its anti-fracture efficacy is, however, poorly documented.

Fluoride is a potent osteoblast mitogen, which stimulates bone formation and significantly increases BMD. It also causes a dose-dependent mineralisation defect and has not been shown to reduce fracture risk.

Future treatments

New antiresorptives

Recent advances in osteoclast biology, in particular our understanding of the RANKL/OPG system, lysosomal cysteine proteinases and intracellular acidification, have led to the development of a number of new and exciting antiresorptive agents – these include OPG analogues, RANKL inhibitors, disintegrins which bind and inhibit osteoclast $\alpha V^{\beta 3}$, carbonic anhydrase II (CA2) modulators, Cathepsin K inhibitors and more.

New bone formation stimulators

Mitogens and growth factors are difficult to target exclusively to bone and therefore have limited therapeutic potential at present. Sclerostin is however a novel bone morphogenetic protein (BMP)-antagonist, expressed exclusively in bone. Mutations in the SOST-gene which codes for sclerostin, results in the sclerotic bone disease called sclerosteosis – inhibitors of sclerostin have been developed and are now being tested as novel anabolic agents.

A rational choice of drug therapy

Given the clinical, histological and biochemical heterogeneity of osteoporosis, no "best drug scenario" to optimally treat this condition is appropriate. In fact, fracture reduction has not been assessed in head-to-head trials, so it is not possible to compare the efficacy of bone active agents directly. The choice of drug(s) to manage osteoporosis should therefore be determined by:

i. The ***nature of the disease*** (e.g. calcium/vitamin D for mild osteopenia; bisphosphonates for osteoporosis; and the addition of an anabolic agent in patients with severe osteoporosis
ii. The ***patient profile*** (e.g. bisphosphonates or strontium ranelate in otherwise healthy subjects requiring a bone specific agent; HRT in young postmenopausal women with troublesome menopausal symptoms, SERMS for those at risk of breast cancer etc.),
iii. ***Cost-effectiveness, side-effects*** and ***availability*** of drugs (Table V)

Table V: Rational Choice of Therapy

• Nature of the Osteoporosis
– Severity of the Osteopenia
– Presence of Fractures
– Turnover / Sites
– Response to Therapy
• The Patient
– Healthy, requiring a Bone-Specific Drug
– Menopausal Symptoms
– Risk of Breast Cancer
– Frail Elderly / Life Expectancy
– Personal Preferences / Willingness
• Cost-Effectiveness / Side-Effects
• Availability

Monitoring

Clinical monitoring to assess efficacy (height, kyphosis), side-effects and compliance is essential.

Densitometry follow-up every 18-24 months (within 12 months in patients with glucocorticoid OP) is important for patient motivation and to monitor compliance and efficacy. Antiresorptive therapy fills in the remodelling space (bone which has been resorbed yet not replaced) which accounts for the 5-10% increase in BMD during the 2-3 years after initiating treatment with these drugs. The magnitude of the increase depends in part on initial bone turnover – absence of an increase in BMD should not be seen as a therapeutic failure.

Morphometry. Vertebral imaging (x-rays, LVA IVA) every ± 3 years is essential to assess the efficacy of treatment.

Biochemistry. Biomarkers of bone turnover hold much promise, but large biological and technical variations limit their routine use in individual patients.

Conclusion

Recent advances in the field of osteoporosis have involved both fundamental conceptual changes in our understanding of its definition and natural evolution on the one hand, as well as a number of technological developments on the other. The former have highlighted the limitations of a largely BMD-based diagnosis; emphasized the importance of bone quality and BMD-independent risk factors of osteoporosis; and stressed the need to distinguish between simple diagnostic criteria and often complex interventional thresholds. The latter have largely confirmed the efficacy and safety of antiresorptive drugs like the bisphosphonates in large randomised controlled trials (RCTs); cautioned against the use of agents which had not previously been subjected to rigorous RCTs (e.g. use of HRT prior to the WHI); and included the launch of new anabolic (teriparatide) and dual-action (strontium ranelate) drugs. Improved understanding of bone biology has further led to the development of a vast array of bone active drugs which will enable the care physician to efficiently and safely treat even advanced cases of osteoporosis in a rational and scientific way.

See CPD Questionnaire, page 42

Ⓟ This article has been peer reviewed

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