NOFSA Guideline for the Diagnosis and Management of Osteoporosis

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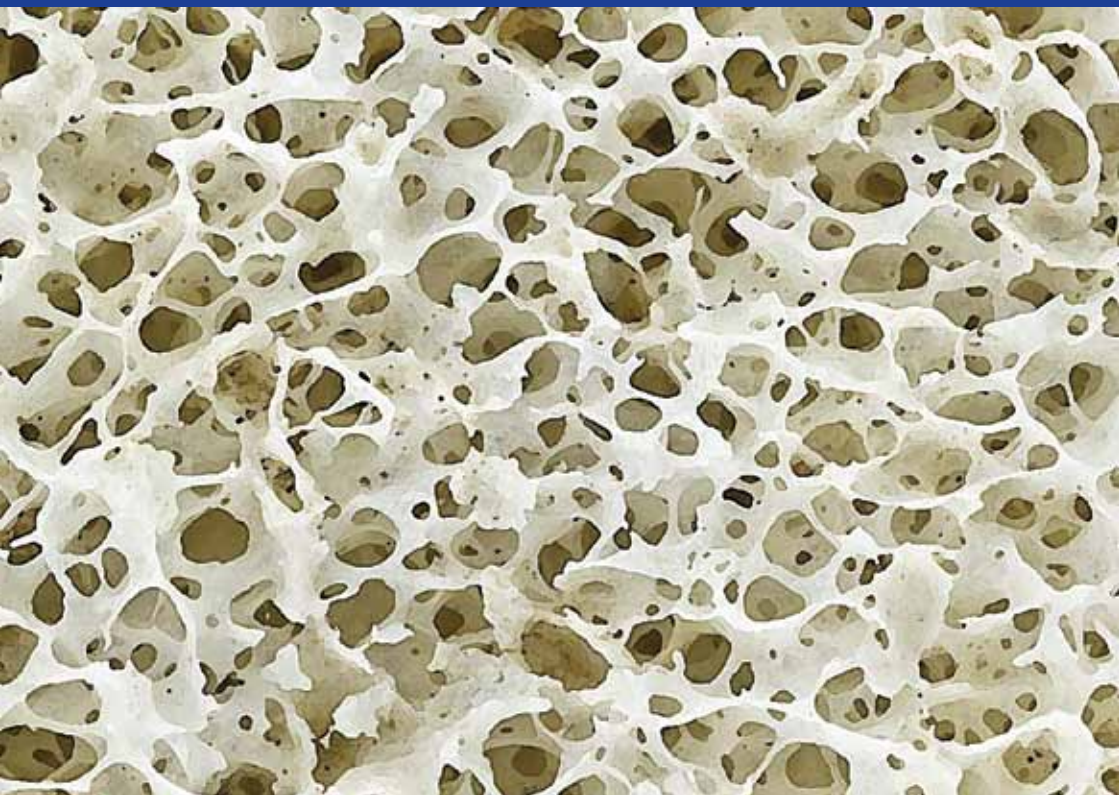

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for the National Osteoporosis Foundation of South Africa (NOFSA)

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Stephen Hough, Brynne H Ascott-Evans, Susan L Brown, Bilkish Cassim, Tobie J de Villiers, Stan Lipschitz, John M Pettifor and Ernst WW Sonnendecker

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Endorsement

This guideline has been fully endorsed by the following societies and organisations:

Association for Dietetics in South Africa (ADSA)

Pharmaceutical Society of South Africa (PSSA)

Radiological Society of South Africa (RSSA)

Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

South African Geriatrics Society (SAGS)

South African Menopause Society (SAMS)

South African Orthopaedic Association (SAOA)

South African Rheumatism and Arthritis Association (SARAA)

South African Society of Obstetricians and Gynaecologists (SASOG)

South African Society of Physiotherapy (SASP)

Contents

SUMMARY AND RECOMMENDATIONS

This is a summary of the detailed guideline which follows. All headings, subheadings, tables and figures refer to that guideline.

Osteoporosis is a common and costly disease which carries a significant morbidity and mortality. The lifetime risk of a fracture in Caucasian women is 30-40%, and about 20% in men. Up to 20% of hip fracture victims die within one year, and more than 50% never regain the functional ability to lead an independent life. In South Africa, the incidence of osteoporosis in our white, Asian and mixed-race populations appears to be similar to that of developed countries, although no accurate fracture data exist. As in the USA, hip osteoporosis is less prevalent in our black populations, although vertebral bone mass, and possibly also fracture prevalence, in black and white South Africans appear to be similar. Further research on this important topic is clearly required.

1. SCOPE AND BACKGROUND

This document is an update of the clinical guideline published by the National Osteoporosis Foundation of South Africa (NOFSA) in 2000, which aims to improve the overall efficacy of the diagnosis and management of patients with, or at risk of, osteoporosis. The guideline targets all health care workers. It should serve as a guide for clinical decision making and not as rigid, prescriptive rules on patient management.

2. METHODS OF DEVELOPMENT

To compile this guideline, systematic reviews and the highest level of evidence (randomised controlled trials (RCTs) and meta-analyses of RCTs) were used as far as possible, and isolated descriptive studies and expert opinions were largely ignored. Data sources consulted included electronic databases (e.g. MEDLINE, PubMed, Embase), systematic reviews (e.g. Cochrane Library) and handsearched journals, including recently published guidelines on osteoporosis. Recommendations were formulated and final decisions were made by formal consensus.

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria were used to describe the quality of evidence and the strength of recommendations.

GRADE uses four categories of quality: *High* (ØØØØ), *Moderate* (ØØØO), *Low* (ØØOO), and *Very Low* (ØOOO). The strength of recommendation was largely based on the quality of the evidence. We used a score of 1 or *"we recommend"* for strong recommendations, and a score of 2 or *"we suggest"* for weak recommendations.

3. ABBREVIATIONS

A full list of abbreviations used in the text is provided (see Chapter 3 of full guideline).

4. DEFINITION OF OSTEOPOROSIS

Osteoporosis is currently defined by the World Health Organization (WHO) as a systemic skeletal disease characterised by low bone mass (readily measured as bone mineral density, BMD) and microarchitectural deterioration of bone tissue (difficult to assess), with a consequent increase in bone fragility and susceptibility to fracture, which usually involves the wrist, spine, hip, pelvis, ribs or humerus. The National Institutes of Health (NIH) define osteoporosis as a disease characterised by a "decreased bone strength" and propensity to fracture.

4.1 The WHO definition

In 1994, the WHO proposed four diagnostic categories largely based on a subject's bone mineral density (BMD), expressed in relation to the young adult reference mean (the T-score), viz (i) normal, (ii) low bone mass or osteopenia, (iii) osteoporosis and (iv) severe osteoporosis (Table I, p 43). These criteria were updated in 2008 and differ from those proposed in 1994 by specifying a single reference site (the femoral neck), providing a young normal reference range for women *and* men (the NHANES III reference data for femur neck measurements in *women* aged 20-29 years), and by accommodating diagnostic criteria for men. This subject, including the selection of the most appropriate site(s) to measure BMD, the use of appropriate reference data, and the recommended criteria to diagnose osteoporosis in men, women, children and different ethnic populations, is discussed in some detail later in the full guideline (see 6.3, p 61).

4.2 Limitations of present definitions of osteoporosis

While the WHO classification has provided a practical basis to identify postmenopausal Caucasian women at risk of fracture, it has limitations:

- A single measurement of BMD has a relatively high specificity (±85%) to predict fracture risk, but lacks sensitivity, and less than 50% of patients with a known osteoporotic fracture have a BMD value that is in the so-called osteoporosis range (i.e. T-score below –2.5).

- The WHO criteria are based on data obtained in healthy Caucasian postmenopausal women, employing dual energy X-ray absorptiometry (DXA) of the axial (spine, hip) skeleton. Extrapolation of these criteria to other populations (young individuals, children, males, black people) assessed with different techniques (quantitative ultrasound, QUS; quantitative computed tomography, QCT), at different skeletal sites, is not acceptable. T-scores cannot be used interchangeably between the different techniques available to measure BMD.
- The exclusively BMD-based diagnostic approach of the WHO classification does not include extraskeletal risk factors like the propensity to falls, nor does it assess qualitative risk factors (e.g. bone turnover) which significantly influence overall bone strength. A low BMD may also result from metabolic bone diseases other than osteoporosis (e.g. primary hyperparathyroidism, osteomalacia), which are treated differently to osteoporosis.
- Finally, the four *diagnostic categories* developed by the WHO for postmenopausal Caucasian women cannot be employed as the only *intervention thresholds* for all (see below).

5. DETERMINANTS OF SKELETAL STRENGTH AND FRACTURE RISK

Bone strength is largely determined by bone mass (bone mineral density, BMD), which is a function of (i) peak bone mass attained during early adulthood, (ii) age-related bone loss, and (iii) total duration of bone loss (Figure 1, p 47). Peak bone mass is largely determined by heredity, body size and gender, while age-related (involutional) bone loss results mainly from menopausal hormone deficiency (which increases bone resorption) and ageing (which is largely attended by impaired bone formation). If lifestyle factors (poor nutrition, lack of physical exercise, smoking, alcohol abuse), systemic disease (Table II, p 49) and/or the use of bone-toxic drugs (Table VII, p 99) are superimposed on this age-related bone loss, significant osteoporosis may ensue (Figure 2, p 52).

Bone strength is also influenced by qualitative structural and functional properties which include (i) macroarchitectural factors (e.g. bone size, geometry), (ii) microarchitectural factors (e.g. cortical thinning and porosity; trabecular size, number and connectivity), (iii) bone turnover, and (iv) material properties of bone (e.g. collagen composition and cross-linking; primary and secondary mineralisation; micro-damage repair). Unlike BMD, which can be readily measured, bone quality is difficult to assess.

6. DIAGNOSIS OF OSTEOPOROSIS

Currently, the diagnosis of osteoporosis is established in two ways: (i) by *measurement of bone mineral density (BMD),* and (ii) on the basis of a history or evidence of a *fragility*

fracture. A reduction in vertebral height of at least 20% or 4 mm is required for the diagnosis of a vertebral fracture.

6.1 Diagnostic techniques

A variety of techniques are available to measure bone mass, to detect osteoporotic fractures, and/or to assess bone strength and fracture risk. These include:

- Conventional skeletal radiology (see 6.1.1, p 53).
- Dual energy X-ray absorptiometry (DXA); vertebral fracture assessment (VFA) and hip structure analysis (HSA) (see 6.1.2, p 54).
- Quantitative CT (QCT) and high resolution CT (HRCT) (see 6.1.3, p 56).
- Quantitative ultrasound (QUS) (see 6.1.4, p 56).
- Tools to measure the peripheral skeleton, e.g. peripheral quantitative CT (pQCT), peripheral DXA (pDXA) (see 6.1.5, p 57).
- Other specialised techniques to assess bone density and/or structure (see 6.1.6, p 57).

6.2 Clinical application of bone mass measurement

Bone mass measurements are largely employed to make a diagnosis of osteoporosis and to aid in the decision whether or not to initiate treatment with a bone-active agent (Figure 3). A limited role for BMD measurements in therapeutic decision making and in patient follow-up exists (see 6.2.1–6.2.6, p 57-61).

6.3 NOFSA recommendations on the diagnosis of osteoporosis

a. A ***diagnosis of osteoporosis***, based on a bone mineral density (BMD) measurement or presence of a fragility fracture, should be ***confirmed before initiating treatment*** with bone-active drugs (GRADE 1/ØØOO).

b. Given its accuracy, precision, low radiation dose, short scanning time, ability to predict fracture and validation in the WHO classification of osteoporosis, ***central (axial) dual energy X-ray absorptiometry (DXA)*** *should be used to assess BMD and to diagnose osteoporosis*. It is also the technique of choice to assess rates of bone loss or gain (GRADE 1/ØØØO). We do not recommend the use of other techniques, including ***quantitative CT (QCT)*** and ***quantitative ultrasound (QUS),*** for the diagnosis of osteoporosis. This does not preclude their use to assess fracture risk, particularly if central DXA is not available. Results from these technologies should be interpreted with caution and cannot be applied to the T-score-based WHO diagnostic classification of osteoporosis (GRADE 1/ØØØO).

c. An evidence-based recommendation cannot be made on the most suitable ***skeletal site to measure BMD***. It is suggested that the recommendations of the International Society for Clinical Densitometry (ISCD) (see 6.1.2.1, p 54) to use BMD values at the spine, total femur and femur neck (or distal radius if measurements at the spine and hip are invalid) be employed, and to use the lowest BMD value recorded (GRADE 2/ØOOO).

d. ***Interpretation of BMD results:*** A diagnosis of osteoporosis should be based on the lowest BMD value obtained. BMD results in Caucasian, ***postmenopausal women*** should be expressed as T-scores employing the WHO criteria (Table I, p 43) and the NHANES III reference databank. Z-scores should be used in ***premenopausal women and men under 50 years of age*** (Figure 3, p 58) (GRADE 1/ØØØO).

e. The risk of fracture in ***men over 50 years of age*** is substantially lower for a BMD within their own reference range. It has, therefore, been suggested that either a lower absolute value of BMD be used (e.g. female values) as a cut-off in men, or that different diagnostic criteria be used (e.g. a T-score of -3.0 instead of -2.5). It is suggested that the new WHO recommendation, to employ female reference data to determine T-scores in males over the age of 50 years, be used (GRADE 2/ØOOO).

f. The diagnosis of osteoporosis in ***local black populations*** requires local BMD reference values (GRADE 1/ØØØO). Mean BMD values in the South African black population appear to be lower than those of African Americans used by DXA manufacturers. It is suggested that, until local reference values become available, reference data for Caucasian females be used for subjects of all races (GRADE 2/ØOOO).

NOFSA recommendations

g. The diagnosis of osteoporosis in ***children*** should be based on a low BMD (Z-score ≤ -2.0 after adjustment for gender, body size, pubertal status (Tanner stage) and ethnicity) *plus* a significant fracture history: one long bone fracture of the lower extremities, or two or more long bone fractures of the upper extremities, or vertebral compression fractures (GRADE 1/ØØØO).

h. ***BMD should be performed*** in women after age 65 years and in men over age 70 years, regardless of additional risk factors. In younger individuals, a BMD measurement is acceptable at any time if the indication (Table III, p 64) is valid.

i. Routine follow-up scans should be performed every 18–24 months, although earlier follow-up may be indicated for conditions characterised by rapid initial bone loss e.g. glucocorticoid–induced osteoporosis (GIOP) (GRADE 1/ØØØO).

j. ***Evidence of vertebral fracture*** should be sought in all patients who qualify for a bone mass measurement. Standard X-rays or DXA-based vertebral fracture assessment (DXA-VFA) can be used for this purpose (GRADE 1/ØØOO). The Genant semi-quantitative system (Grade 1–3) should be used to classify fractures (GRADE 1/ØØØO).

7. FRACTURE RISK ASSESSMENT

No more than 10-44% of women with an osteoporotic fracture have a bone mineral density (BMD) value within the so-called osteoporosis range (T-score below -2.5), and most fractures occur in individuals with osteopenia (T-score -1.0 to -2.5). The sensitivity to identify fracture risk can be increased by lowering the BMD threshold to a T-score of -2.0, but this would significantly decrease the specificity of the test. A better alternative to improve the gradient of risk (GR) is to combine the BMD measurement with other risk factors, which could include one or more of the following:

- Clinical risk factors (CRFs).
- Assessment of bone turnover (biochemistry, bone histology).
- Others (quantitative ultrasound, QUS; genetic markers).

7.1 Clinical risk factors

Numerous clinical risk factors (CRFs) for osteoporosis have been identified, some of which are listed in Table II (p 49). CRFs generally lack sensitivity and may differ among patient populations. They do, however, impact on one another and are *additive* in predicting fracture. Recent meta-analyses have suggested that advanced age, a prior fragility fracture, a low body weight (body mass index, BMI), and a family history of osteoporotic hip fracture are the major CRFs in most healthy postmenopausal women. Obviously the secondary osteoporoses, including hypogonadism and glucocorticoid-induced osteoporosis (GIOP), become more

important in specific settings, while other lifestyle factors (e.g. alcohol and smoking) may prevail in certain populations. The propensity to falls becomes increasingly more important with ageing in women, as well as in men.

7.2 Assessment of bone turnover

A high bone turnover is not only associated with increased bone loss and a low BMD, but also impairs bone quality and increases fracture risk independently of BMD. Bone turnover can best be assessed by analysing (i) biochemical markers of bone turnover, or (ii) quantitative bone histology.

7.2.1 Bone turnover markers

Bone turnover markers (BTMs) are classified as markers of bone formation and markers of bone resorption (Table IV, p 70). Bone formation is assessed by measuring the enzymatic activity of osteoblasts (e.g. bone-specific alkaline phosphatase, BSALP), bone proteins (osteocalcin) or fragments of procollagens released during bone formation (the C- and N-terminal propeptides of type I collagen, PICP and PINP). Resorption markers are either degradation products released during osteoclastic resorption of bone (C-terminal telopeptides of D-Pyr (CTX), N-terminal telopeptides of D-Pyr (NTX), carboxyterminal telopeptides (ICTP) and pyridinolines), or osteoclast regulatory protein markers.

BTMs have been used to (i) identify those at risk of rapid bone loss, (ii) identify those at risk of fracture, independent of BMD, (iii) help rationalise the type of osteoporosis therapy, and (iv) monitor the response to therapy. Evidence exists that, to assess fracture risk, the combination of a BMD measurement plus BTM data will enhance the sensitivity of a BMD alone. Unfortunately, technical and biological variations in the measurement of BTMs complicate the assessment of *individual* patients.

7.2.2 Bone biopsy

Use of time-spaced tetracycline-labelled quantitative bone histology is invaluable to diagnose osteomalacia. A transiliac bone biopsy is, however, an invasive procedure, and is not indicated in the vast majority of patients with osteoporosis.

7.3 Ultrasonic bone assessment

There is general agreement that quantitative ultrasound (QUS) cannot replace central dual energy X-ray absorptiometry (DXA) to diagnose osteoporosis, or to follow up patients with this disease. The value of QUS as surrogate method to estimate BMD or to assess fracture risk independently of BMD has, however, been documented in numerous studies. The value of combining BMD and QUS to improve sensitivity has been unequivocally proven in recent studies,

most notably the EPISEM database of 12,958 elderly women. It remains unclear as to whether or not the addition of QUS to the combination of BMD values *plus* independent CRFs is cost effective.

NOFSA recommendations

7.4 NOFSA recommendations on fracture risk assessment

a. ***Clinical risk factors (CRFs)*** should always be included in any assessment. Meta-analyses of RCTs have shown that the combined use of CRFs and bone mineral density (BMD) significantly improves the gradient of risk (GR) compared with BMD alone (GRADE 1/ØØØØ).

c. Those ***CRFs identified by the WHO,*** namely prior fragility fracture, advanced age, a low body mass, a family history of osteoporotic hip fracture, smoking, excessive alcohol intake (three or more drinks per day), diseases known to adversely affect bone and bone-toxic substances, like glucocorticoids, should be used to identify subjects at risk (GRADE 1/ØØØO). In addition, we suggest that the following CRFs should also be included: (i) evidence of inadequate calcium/vitamin D nutrition, and (ii) high fall propensity (GRADE 2/ØØOO).

d. ***Local research on CRFs*** is urgently required (GRADE 1/ØØØØ).

e. ***Bone turnover markers (BTMs) should not be used routinely***, but in *selected* cases only (e.g. to help decide whether to initiate treatment with bone-active drugs or not, or to assess adherence to therapy) (GRADE 1/ØØØO).

f. ***The choice of BTM*** is dependent on availability, costs, technical considerations (accuracy, precision, stability, clearance) and the indication for the measurement. Bone-specific alkaline phosphatase (BSALP) and the telopeptides (CTX and NTX) appear to enjoy the widest appeal currently, but osteocalcin and deoxypyridinoline (D-Pyr) are acceptable alternatives. No recommendation can, however, be made as to which BTM should be used locally. An urgent need exists to assess the local availability, standardisation and quality control of BTMs, and it is recommended that NOFSA establishes a working group to examine this (GRADE 1/ØØØO).

g. ***Interpretation of BTM data*** is made difficult by the lack of any universal definition of what constitutes a "high bone turnover". Assay-specific reference values for various patient populations are generally employed, but are often not sensitive enough to use as intervention cut-points. We suggest that BTM values above the *premenopausal* reference range be used as an intervention cut-point in pre- and postmenopausal women (GRADE 2/ØØOO).

h. ***Bone biopsy is not indicated in the vast majority of patients*** with osteoporosis, but should be considered when osteomalacia is suspected.

i. ***In the absence of central dual energy X-ray absorptiometry (DXA), quantitative ultrasound (QUS) plus CRFs can be employed to make therapeutic decisions.*** In agreement with the ISCD and other guidelines, we recommend that QUS of the heel be used, *in conjunction with CRFs,* to decide on therapeutic intervention (GRADE 1/ØØOO). Device-specific thresholds should be employed and results should not be applied to the T-score-based WHO diagnostic classification of osteoporosis (GRADE 1/ØØØO).

j. ***Combining QUS and DXA/BTMs to improve fracture risk assessment cannot be recommended at this stage***. We have taken cognisance of recent reports advocating the value of incorporating QUS into a CRF-BMD programme to stratify fracture risk, but cannot recommend the routine combination of QUS and DXA at this stage (GRADE 1/ØØOO). Furthermore, data from the EPIDOS and SEMOF studies revealed that, whereas QUS and BTMs were both useful to discriminate between non-vertebral fracture cases and controls, the combination of these tests was no better than either test alone. Combining QUS and BTMs can, therefore, not be recommended to improve fracture risk assessment (GRADE 1/ØØOO).

8. AN INTEGRATED APPROACH TO FRACTURE RISK ASSESSMENT

8.1 Diagnostic criteria vs. intervention thresholds

The diagnosis of osteoporosis centres on the assessment of bone mass and quality. Since the latter cannot readily be measured, the diagnosis of osteoporosis depends at present on the measurement of bone mineral density (BMD). The importance of risk factors, other than BMD, which predispose to fracture has been emphasised. For this reason, there is a distinction to be made between the diagnosis of osteoporosis and the assessment of risk. This, in turn, implies a distinction between *diagnostic criteria* and *intervention thresholds*. Whereas the former have been firmly established, the latter remain controversial.

Most guidelines agree that patients with T-scores below -2.5 should be treated, and that patients with T-scores above -1.0 should not. The major controversy involves the group with T-scores between these values, i.e. those with osteopenia. In this regard, it should be noted that such decisions are complex and do not only depend on *absolute risk*, but also on the *patient profile* (age, gender, life expectancy and willingness to consider treatment), as well as the *efficacy and costs* of available treatment.

Worldwide, two basic case-finding intervention strategies have been employed. The International Osteoporosis Foundation (IOF) model, adopted by the Royal College of Physicians and others, is based on clinical risk factors (CRFs) which dictate the need for BMD testing and, if a T-score of less than -2.5 is found, the patient should be treated. The

American National Osteoporosis Foundation (NOF) model, published in 1998, recommends treatment for postmenopausal women with a T-score below -2.0, or a T-score below -1.5 in the presence of clinical risk factors (CRFs). The advent of the new WHO risk platform (FRAX®) has created the possibility of a new global case-finding strategy.

8.2 Expression of fracture risk

See the full guideline (p 80) for details

8.3 The new WHO risk platform (FRAX®)

8.3.1 The FRAX® tool

This new WHO assessment tool has identified a number of robust CRFs for the development of osteoporosis, based on an analysis of 12 study populations (> 60,000 subjects). These include age, gender, BMI, prior fragility fracture, parental history of osteoporotic hip fracture, long-term (more than three months) exposure to systemic glucocorticoids, high alcohol intake (three or more units per day), smoking, rheumatoid arthritis and other putative causes of secondary osteoporosis. The relative weights and interactions of the CRFs are quantified, along with femoral BMD.The model output is the estimated 10-year probability of the occurrence of either a hip fracture alone, or the major osteoporotic fractures combined (hip, spine, wrist and humerus). The FRAX® tool is freely available online to all clinicians and health care professionals (www.shef.ac.uk/FRAX).

8.3.2 Clinical utilisation of the FRAX® tool

The FRAX® tool can be used, *with or without BMD data*, to assess risk and to indicate whether osteoporosis treatment is indicated or not. Although the tool is promoted by the WHO to assess all patients at potential risk of osteoporosis, organisations like the American NOF use the tool only to evaluate that subset of patients with DXA-proven *osteopenia* (see below).

8.3.3 Strengths and limitations of the FRAX® tool

One of the strengths of the model is its utilisation of not only the relative importance of different CRFs, but also the fact that *CRFs* are *interactive* and *additive* in their predisposition to fracture. Limitations of the model include the fact that epidemiological data on the incidence of hip fracture and mortality rates in specific populations are required before the model can be applied. Further, the model provides an estimate of the 10-year absolute fracture risk and was never intended to suggest intervention thresholds. If these are required, a cost-efficacy analysis to estimate the levels of fracture risk above which it is

reasonable to consider treatment must be performed for a particular population. The model also does not include a number of important risk factors (e.g. vertebral fracture, falls, bone turnover markers), uses only femoral and not vertebral BMD, and cannot evaluate individuals below 40 years of age.

8.4 NOFSA recommendations on an integrated approach to managing osteoporosis in postmenopausal women, and men over the age of 50 years

a. ***We recommend that treatment should be considered when a prior fragility fracture is present,*** regardless of the results of a BMD measurement. This approach is supported by both the American NOF and the WHO/European Guidance (GRADE 1/ØØØO). The WHO strategy does not specify the nature of the fragility fracture, whereas the new NOF guide specifically refers to prior hip or vertebral fractures. It is suggested that treatment be initiated on the basis of a typical osteoporotic fracture, i.e. wrist, spine, hip, pelvis, rib, or humerus (GRADE 2/ØØOO). This NOFSA recommendation does not imply that a BMD measurement should not be performed whenever possible, since it adds significantly to the overall management of patients with osteoporosis (see 6.2, p 57).

b. ***We recommend that treatment should be considered when the DXA T-score is ≤ -2.5 at the hip or spine*** (GRADE 1/ØØØO).

c. ***We recommend that treatment should also be considered in patients with osteopenia (T-score -1.0 to -2.5) under certain circumstances.*** In these subjects, the use of FRAX® could be considered once epidemiologic data on fracture incidence and mortality in this country become available. In the interim, it is suggested that those major clinical risk factors (CRFs) previously identified be utilised in a simple algorithm (Figure 4, p 86) to determine the need for treatment (GRADE 2/ØØOO). If the need to intervene is still not apparent, a decision can be made to either use bone turnover markers (intervene if BTM values exceed the upper limit of the *premenopausal* reference range), or to adopt a conservative wait-and-see attitude and to reassess in 18-24 months (GRADE 2/ØØOO). We do not recommend the addition of other risk assessment tools, in particular quantitative ultrasound (QUS) or quantitative CT (QCT), at this stage (GRADE 1/ØØOO).

g. ***We strongly recommend the need to assess the incidence of osteoporotic fractures in South African populations,*** following which a health economic strategy should be formulated for the treatment of osteoporosis in this country (GRADE 1/ØØØØ).

9. CLINICAL AND LABORATORY ASSESSMENT

A detailed clinical evaluation and appropriate laboratory assessment are required in all patients prior to the initiation of treatment for osteoporosis. The aim of this assessment (Figure 5, p 89) is to:

- Confirm the diagnosis of osteoporosis and rule out other metabolic bone diseases (e.g. primary hyperparathyroidism, osteomalacia) as the cause of the low BMD.
- Identify secondary causes of osteoporosis (Table II, p 49).
- Identify lifestyle factors which may affect bone health adversely (e.g. diet, alcohol, smoking, sedentary lifestyle), and risk factors for falls (Table VIII, p 102).
- Characterise the severity, skeletal sites involved and nature of the osteoporosis.
- Assess patient preferences, compliance, potential drug side-effects, and financial resources.
- Rationalise and initiate therapy.
- Use baseline data to monitor the response to therapy and to reassess therapeutic options.

NOFSA recommendations

9.3 NOFSA recommendations on the assessment of patients with osteoporosis

a. ***Serum calcium, phosphate, albumin, creatinine, total alkaline phosphatase (ALP) and parathyroid hormone (PTH)*** levels should be assessed in every patient with apparent osteoporosis, to exclude primary hyperparathyroidism and osteomalacia (GRADE 1/ØØØO). A ***serum 25-hydroxyvitamin D (25OHD)*** level should be obtained in all elderly patients and, in particular, those who are institutionalised, housebound or have low sunlight exposure (including the use of sun blockers, and if covering up for religious reasons), have increased skin pigmentation, are obese, suffer from suspected malnutrition, malabsorption or liver disease, or use drugs that interfere with vitamin D metabolism, like the anticonvulsants.

b. ***Biochemical tests to identify causes of osteoporosis should largely be dictated by clinical assessment*** and few tests should be performed routinely (GRADE 1/ØØØO).

c. A limited number of ***routine tests*** are, however, justifiable in order to identify underlying causes of osteoporosis. These include a full blood count and ESR, serum protein electrophoresis, TSH level, sex hormone levels in males, or females when the menopausal state is uncertain, and a urine calcium (GRADE 2/ØOOO).

d. A number of ***optional tests***, which should be considered under specific clinical circumstances, are listed in Table V (p 92) (GRADE 2/ØOOO).

10. NON–PHARMACOLOGICAL MANAGEMENT OF OSTEOPOROSIS

Non- pharmacological measures to prevent osteoporotic fractures are essentially aimed at (i) improving bone strength and (ii) preventing falls.

10.1 Non-pharmacological measures to improve bone strength

10.1.1 Healthy eating plan

Many nutritional factors have been implicated as possible causes of osteoporosis. A healthy eating plan, containing the correct amount of energy and all essential nutrients (including calcium and vitamin D), with sufficient but not excessive protein, appears to be the most important dietary measures to help prevent this disease.

The following points regarding a balanced diet should be borne in mind:

- Calcium is important for the attainment of peak bone mineral density (BMD) in the young and to prevent bone loss in the aged. Recommendations for optimal calcium intake are shown in Table VI (p 96).
- Severe prolonged vitamin D deficiency induces osteomalacia, but less marked deficiency causes secondary hyperparathyroidism, an increased bone turnover and osteoporosis.
- Protein-energy malnutrition decreases bone formation, and is associated with hypogonadism, muscle weakness and an increased risk of falling. High intakes of fibre, phytate and oxalate impair intestinal absorption of calcium, whereas a high sodium intake enhances urinary calcium excretion. Caffeine may promote urine calcium wasting.

10.1.2 Physical exercise

Adequate physical exercise is essential for normal bone formation. A specified walking programme (5 km per day, four days per week, at a brisk pace) is necessary to improve hip BMD, while specific resistance exercises for the lower back have been shown to improve vertebral BMD. Excessive exercise (particularly when coupled with poor energy and calcium intake), on the other hand, may result in functional hypogonadism and bone loss.

10.1.3 Limit alcohol consumption and stop smoking

Chronic alcohol consumption, of three or more units per day, directly inhibits osteoblastic bone formation and also causes hypogonadism, hypercortisolaemia, liver disease and hypovitaminosis D. Alcohol abuse may result in osteoporosis and/or osteomalacia. Smoking is an independent risk factor.

10.1.4 Avoid bone-toxic drugs

A number of drugs, other than alcohol and smoking, predispose to fracture by reducing bone strength and/or by predisposing to a fall (Table VII, p 99). Note that drugs like the anticonvulsants (which promote the catabolism of 25OHD) may cause not only osteoporosis, but also osteomalacia.

Chronic (more than three months) glucocorticoid use is a major risk factor for the development of osteoporosis. Early on, bone resorption is stimulated, but later a marked direct suppression of bone formation (and resorption) results in predominantly low-turnover osteoporosis. Additionally, glucocorticoids decrease circulating sex hormone levels, inhibit gastrointestinal absorption of calcium, promote renal calcium wasting and may cause a myopathy which predisposes to falls.

Glucocorticoid-induced osteoporosis (GIOP) develops very rapidly. About 50% of the total bone loss occurs within the first six to 12 months of steroid treatment. If prophylactic therapy is to be of value, it should, therefore, be initiated early. Since glucocorticoids not only decrease BMD, but also adversely influence bone quality, fractures tend to occur at a higher BMD than in subjects with primary osteoporosis. It has been suggested that pharmacological intervention should be contemplated with T-scores of around -1.5 to -2.0.

10.2 Prevention of falls

A number of systematic literature reviews have revealed that a relatively small number of risk factors for falls (Table VIII, p 102) emerge consistently: medication, particularly sedatives, hypnotics and benzodiazepines; cognitive dysfunction; gait and balance disorders; weakness and immobility; or a history of falls will individually increase risk between two- and fivefold. A systematic approach to the prevention of falls is important.

Effective interventions for fall prevention include: assessment and multifactorial component interventions in high risk fallers; possible withdrawal of psychotropic medications; professionally delivered exercise programmes; home safety interventions, particularly for persons with visual impairments; cataract corrective surgery; and pacemakers for carotid sinus hypersensitivity.

10.3 NOFSA recommendations on the non-pharmacological management of patients with osteoporosis

a. ***The intake of adequate amounts of calcium (1,000–1,200 mg/day) and vitamin D (800–1,000 IU/day)*** should be ensured. Although every effort should be made to obtain this from the diet (low-fat dairy), it is often not possible (food fortification is rare in this country and ample ultraviolet exposure is often difficult to achieve), and supplementation may, therefore, be required (GRADE 1/ØØØO).

b. ***Additional vitamin D is required during pregnancy and lactation.*** It is suggested that at least 2,000 IU vitamin D per day is necessary during pregnancy and lactation (GRADE 1/ØØØO).

c. ***Obtain serum 25OHD levels*** in those subjects in whom vitamin D deficiency is likely to be present, viz elderly institutionalised, sun-protected (religious reasons or sun screens), dark-skinned, obese, or malnourished individuals. Interpretation of 25OHD levels is controversial and discussed in some detail in the full guideline. It is suggested that a serum 25OHD level > 30 ng/ml indicates a vitamin D replete state, a level < 20 ng/ml suggests vitamin D deficiency, and a level between 21 and 29 ng/ml reflects vitamin D insufficiency (GRADE 1/ØØOO). Patients with vitamin D deficiency osteomalacia invariably have 25OHD levels below 5-10 ng/ml.

d. ***Monitor urine calcium excretion*** in subjects on high doses of vitamin D, or those with a previous history of kidney stones (GRADE 1/ØØOO).

e. ***Walking for 5 km at brisk pace, three to four times per week,*** is recommended to improve hip bone strength, while ***back strengthening exercises*** will improve vertebral bone strength. The help of a professional physiotherapist should be considered, particularly in the elderly (GRADE 1/ØØOO).

f. ***Stop smoking and limit alcohol to less than three units per day*** (GRADE 1/ØØOO).

g. ***Prevent falls*** by careful assessment of ***(i) medication*** (particularly sedatives and hypnotics: attempt to withdraw/reduce dose), ***(ii) gait and balance*** (do a "get-up-and-go" test as a screening test), ***(iii) cognition and affect*** (mini mental and depression score), ***(iv) weakness and mobility*** (check quadriceps strength; initiate an exercise programme), ***(v) cardiovascular status*** (including orthostatic hypotension and carotid sinus hypersensitivity), ***(vi) visual acuity and depth perception*** (consider referral to an ophthalmologist), and ***(vii) environmental safety*** (make the home a fall-safe area) (GRADE 1/ØØOO).

NOFSA recommendations

A ***practical algorithm*** for the clinical assessment of falls is presented in Figure 6 (p 107), where the "get-up-and-go" test is largely used as screening test for gait and balance abnormalities. Subjects with abnormalities of gait and balance and/or recurrent falls should be subjected to a ***multifactorial fall management programme***, which includes a full assessment of *(i)* – *(vii)* above.

h. ***Avoid bone-toxic drugs***, and also consider osteomalacia when certain drugs are used (Table VII, p 99).

Glucocorticoid-induced osteoporosis (GIOP) should be prevented and managed by attending to the following:

- It is usually stated that prophylactic therapy is indicated when a glucocorticoid dose ≥ 5 mg per day is used for longer than three months. However, use the lowest effective dose of glucocorticoid, taking due cognisance of marked individual sensitivity and the fact that no dose is safe (GRADE 1/ØØOO).
- Alternate-day regimens and high-dose inhaled steroids are also associated with bone loss (GRADE 1/ØØØO).
- Obtain a baseline bone mass measurement (axial DXA), sex hormones (in men and premenopausal women) and urinary calcium levels. Treat hypogonadism (hormone therapy) and hypercalciuria (indapamide or thiazides) (GRADE 1/ØØOO).
- Adequate calcium and vitamin D intake must be ensured, although their value as monotherapy remains uncertain (GRADE 1/ØØOO).
- Since only 50% of patients on long-term glucocorticoids will develop GIOP regardless of the dose, we recommend that a BMD measurement be obtained in all patients. If a BMD T–score (or Z-score in younger subjects) ≤ -1.5 is documented, treatment with a bone-active drug should be considered. This is particularly relevant if other clinical risk factors (CRFs) for the development of osteoporosis (see 7.1, p 65) are present. If a BMD T- (or Z-) score is ≥ -1.5 and other CRFs are absent, a more conservative approach may be adopted with calcium, vitamin D, an exercise programme and a repeat BMD in six months (GRADE 1/ØOOO).
- Bisphosphonates comprise first-line therapy (GRADE 1/ØØØO).
- Anabolic agents do not have a role in prevention, but should be considered in chronic cases (where turnover is usually suppressed) and in advanced disease (where BMD is very low and fractures are present) (GRADE 1/ØØØO).
- Remeasure BMD, employing central DXA, within one year of initiating glucocorticoid treatment (GRADE 1/ØØØO).

11. PHARMACOTHERAPY OF OSTEOPOROSIS

The specific bone-active drugs used in osteoporosis to prevent bone loss, improve bone strength and reduce the risk of fracture are conventionally classified as inhibitors of bone resorption (anticatabolics), stimulators of bone formation (anabolics), and those with a dual or complex action on bone (Table IX, p 109). Antiresorptive agents (ARAs) generally maintain BMD, whereas a sustained increase in BMD is usually accomplished only with use of the anabolic agents (Figure 7, p 110).

11.1 Inhibitors of bone resorption

Current ARAs include calcium/vitamin D, estrogens, and selective estrogen receptor modulators (SERMs) which largely, although not exclusively, inhibit bone resorption by suppressing osteoclastogenesis, and the bisphosphonates and calcitonin, which inhibit osteoclast activity and promote osteoclast apoptosis.

11.1.1 Calcium and vitamin D

Calcium and vitamin D are modestly useful as monotherapy, but have an additive effect when used with other ARAs and are, therefore, essential adjuncts to all treatments (Table X, p 112).

11.1.2 Hormone therapy

In this guideline, the term "hormone therapy" (HT) is used generically to denote the use of estrogen ± progestin in postmenopausal women. Estrogen therapy alone is referred to as ET, and estrogen in combination with progestogen as EPT.

11.1.2.1 Effects of hormone therapy on bone

Numerous observational and controlled studies have provided evidence of a beneficial effect of HT on BMD and vertebral fracture risk, but we had to wait for the Woman's Health Initiative (WHI) to convincingly document a reduction in the rate of hip fractures. On average, spine BMD after HT increases by about 4-8%, and hip BMD by 3-5%. The increase is transient and reaches a plateau after two to three years (Figure 7, p 110). Fracture risk is reduced at both vertebral and non-vertebral sites by 25–40%. HT is effective in patients with DXA-proven osteoporosis, as well as those with osteopenia. The response is dose-dependent and, although lower-than-normal doses of HT have been shown to improve BMD, no fracture data are available in patients treated as such. The route of administration influences the non-skeletal effects of HT, but does not appear to significantly influence its bone effects.

11.1.2.2 Non-skeletal effects of hormone therapy

Systemic HT is highly effective for the treatment of the ***vasomotor*** and ***urogenital*** symptoms of the menopause. Treatment for seven years with EPT, but not ET, is associated with a small but significant increase in the risk of ***invasive breast cancer***. The risk of ***venous thromboembolism (VTE)*** is doubled with HT, although absolute risk is very small (approximately 2/1,000 per year, in the 50–60 year age group). The risk of ***endometrial cancer*** is increased two- to fivefold in women who use unopposed estrogen. It is, therefore, mandatory that all women with an intact uterus who wish to use HT add a progestin to the estrogen regimen, which largely eliminates the risk. Under certain circumstances, particularly in women over the age of 60 years who are predisposed to vascular disease, HT may increase the risk of ***stroke and coronary heart disease (CHD)***. Contraindications for the use of HT are listed in Table XI (p 118).

11.1.3 Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs), like raloxifene, lasofoxifene and bazedoxifene, are capable of producing estrogen agonist effects in some tissue (e.g bone), and estrogen antagonist effects in others (e.g. breast and endometrium). Raloxifene, registered for the prevention and treatment of osteoporosis in South Africa, causes a very modest increase in BMD and a significant decrease in vertebral fractures, comparable to that of HT or bisphosphonates. There is no evidence that raloxifene decreases the risk of hip fractures.

11.1.4 Bisphosphonates

The bisphosphonates are potent inhibitors of osteoclastic bone resorption. In this country, daily and weekly oral alendronate (branded and generic) and risedronate, as well as zoledronate, which is given as an annual intravenous infusion, are registered for the treatment of osteoporosis (Table XII, p 124). The aminobisphosphonates cause a 2-10% increase in BMD and a marked suppression of bone turnover. The anti-fracture efficacy of the bisphosphonates has been documented in women and men, in most subsets of osteoporosis including glucocorticoid-induced osteoporosis (GIOP), in more than 30 RCTs. The relative risk (RR) of vertebral fractures is generally decreased by about 40–50%, and that of non-vertebral fractures by about 25-35% over periods of three years. Studies on the anti-fracture efficacy of the bisphosphonates have been limited to patients at high fracture risk (i.e. those with a BMD in the osteoporosis range or with prior fracture) and the anti-fracture effect of bisphosphonates in subjects with osteopenia is questionable. Anti-fracture data have been documented for four years and, although 10-year BMD, safety and histomorphometry data are available, information on sustained anti-fracture efficacy beyond four years is unconvincing.

Bisphosphonates are generally well tolerated and the only relatively common side-effect of the oral preparations is ***upper gastrointestinal discomfort***, particularly when the patient reclines within 30–60 minutes of taking the drug. A ***flu-like syndrome*** following the intravenous administration of bisphosphonates may occur, but is usually a first-dose phenomenon. Much concern has been raised about the association between bisphosphonates and ***osteonecrosis of the jaw (ONJ)***. This is, however, hardly ever encountered with the bisphosphonate doses used to treat osteoporosis and occurs most often when patients with underlying malignancy are treated with intravenous bisphosphonates in doses 10-fold higher than those used to manage osteoporosis. ***Atypical fragility fractures (AFFs)*** may be a complication of chronic (longer than five to 10 years) bisphosphonate use in susceptible patients, although a causal relationship has not been established beyond doubt.

11.1.5 Calcitonin

Calcitonin, a peptide hormone produced mainly by the parafollicular C cells of the thyroid, has been shown to improve BMD and reduce vertebral fracture rate. Fracture efficacy data are, however, unconvincing and are confined to the spine.

11.1.6 *NOFSA recommendations on the use of antiresorptive agents*

NOFSA recommendations

a. If adequate amounts of ***calcium*** cannot be obtained from the diet, it must be supplemented. Guard against giving high-dose *calcium* supplementation in those subjects who are already ingesting ample dietary calcium. *Elemental* calcium in supplements varies with the calcium salt used (Table X, p 112). Calcium carbonate should always be taken *with meals* to ensure adequate absorption. Differences in composition between proprietary preparations of calcium supplements are usually not clinically significant. Limit the dose of elemental calcium to 500 mg per day. The prophylactic dose of ***vitamin D*** is 800–1,000 IU per day, but this may increase to 2,000 IU per day or more during pregnancy and lactation (see 10.3, p 105). Cholecalciferol and ergocalciferol are equipotent and either may be used as supplement. If 25OHD levels suggest vitamin D deficiency, higher doses may be required (e.g. 50,000 IU every two weeks) (GRADE 1/ØØØO).

b. ***Hormone therapy (HT)*** has a useful role in the management of osteoporosis. It should be initiated for specific proven *indications*, provided there are *no contraindications* (Table XI, p 118), and should be *individualised*. For example, consider HT for the treatment of postmenopausal subjects in the 50–60 year age range, with vasomotor symptoms, urogenital atrophy or where deemed appropriate, who are at risk of osteoporotic fracture. The latter may be individuals with DXA-proven osteoporosis, but HT is also effective in subjects with osteopenia (GRADE 1/ØØØO).

NOFSA recommendations

c. We do *not recommend* that HT be initiated, nor be continued, *after 60 years of age* for the sake of skeletal protection only. Other bone-active drugs are available for this purpose. Continued use of HT in women older than 60 years may, however, be considered if other treatment options are contraindicated (GRADE 1/ØØOO).

d. If fracture protection is sought, use *doses of HT known to provide fracture protection* (i.e. 0.625 mg conjugated equine estrogen (CE), or equivalent). Lower doses of HT have not been confirmed to reduce fracture risk (GRADE 1/ØØØO). Use the *therapeutic regimen* that is most suitable, e.g. in the patient with an intact uterus, estrogen should be opposed by a progestin to provide endometrial protection. Consider a transdermal preparation in the older individual and in those with a metabolic syndrome phenotype (e.g. obese, hypertriglyceridaemia, glucose intolerant, smokers) (GRADE 1/ØØØO).

e. Approximately 10–20% of patients lose BMD despite HT. *Monitoring* is, therefore, important. Since a rapid reduction in BMD may occur once HT is discontinued, treatment with another bone-active drug at that stage should be considered (GRADE 1/ØØØO).

f. ***Selective estrogen receptor modulators (SERMs),*** like raloxifene, cannot be regarded as standard first-line treatment for osteoporosis, but have a role in selected cases. For example, consider these drugs when predominantly vertebral fracture protection is sought in subjects at risk of breast carcinoma. Use with caution in the vasculopath at risk of stroke (GRADE 1/ØØØO).

g. The use of ***tibolone*** for the treatment of osteoporosis is limited by its safety profile, particularly in subjects at risk of stroke (GRADE 1/ØØØO).

h. ***Phyto-estrogens, progestins,*** and ***testosterone*** cannot be recommended for the sole purpose of fracture protection in women (GRADE 1/ØØØO).

i. In young hypogonadal men, ***testosterone replacement*** should be initiated for non-skeletal benefits. We cannot make a recommendation on whether a bisphosphonate should be added for skeletal protection right from the start, or whether the skeletal response to testosterone treatment only should not first be assessed. We suggest that this decision be individualised, based largely on the severity of the bone disease (GRADE 2/ØOOO).

j. ***Bisphosphonates*** should be regarded as *first-line treatment* for osteoporosis in postmenopausal women, men and in certain secondary osteoporoses, like glucocorticoid-induced osteoporosis (GIOP) (GRADE 1/ØØØØ).

k. Documentation of the anti-fracture efficacy of bisphosphonates has been limited to *patients at high fracture risk*, and their use should, therefore, largely be reserved for those with a BMD T-score ≤ -2.5 and/or a prior fracture (GRADE 1/ØØOO).

l. Oral bisphosphonates should be taken on an *empty stomach with tap water only*, and the patient should refrain from reclining. Oral bisphosphonates should not be prescribed to individuals with known upper gastrointestinal disease. Patients receiving intravenous bisphosphonates should be alerted to the possible development of a transient flu-like syndrome, which may require treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Bisphosphonates are not recommended in patients with a *creatinine clearance < 30 ml/minute*. (GRADE 1 / ØØØO). Although first trimester exposure to bisphosphonates does not appear to pose substantial foetal risk, data are very limited and animal and human studies show that bisphosphonates do cross the placenta. The routine use of *bisphosphonates in pregnancy* cannot, therefore, be recommended (GRADE 1/ØØØO).

m. Patients and, particularly, dentists must be reassured that, when bisphosphonates are used in doses approved for osteoporosis, the incidence of *osteonecrosis of the jaw (ONJ)* is extremely rare and probably not different from that of the general population. A dental examination prior to starting bisphosphonate therapy for osteoporosis is not indicated. If major dental surgery is, however, anticipated, it seems prudent to suggest that this be completed before starting bisphosphonate therapy. In those subjects already receiving a bisphosphonate, dental surgery is not contraindicated. We do not recommend stopping the bisphosphonate, nor employing a biomarker of bone turnover to aid in such management (GRADE 1/ØØOO).

n. Following five years of therapy with a bisphosphonate, we suggest that a *drug holiday* be considered in those who are not at very high fracture risk, in order to prevent the unlikely development of *atypical fragility fractures (AFFs)*. This may be particularly applicable to cases of GIOP. An evidence-based recommendation on the duration of such a drug holiday cannot be made, other than to say that the patient should clearly be followed up. BMD is usually maintained following the discontinuation of a bisphosphonate, but should be monitored after 18-24 months. In subjects with fractures or a BMD that is still in the osteoporosis range (T-score ≤ -2.5), in those with ongoing risk factors, and in those who responded poorly to treatment (e.g. BMD decreased markedly and progressively), treatment with a non-bisphosphonate, like strontium ranelate or teriparatide, should be considered (GRADE 1/ØØOO).

o. There is no apparent difference in the anti-fracture efficacy of the three bisphosphonates registered in this country, *alendronate*, *risedronate* and *zoledronate,* and no particular bisphosphonate is, therefore, recommended. Until further safety and efficacy data become available, we cannot recommend the use of *generic bisphosphonates* (GRADE 1/ØØOO).

p. We cannot recommend the use of ***calcitonin*** as first-line treatment for osteoporosis, and suggest that it be reserved for those individuals who cannot take more effective therapy (e.g. those with a creatinine clearance < 30 ml/minute).

11.2 Stimulators of bone formation

11.2.1 Parathyroid hormone

Administration of low-dose intact PTH, or its 1-34 fragment, teriparatide, causes rapid stimulation of bone formation. Bone resorption is also stimulated by PTH but, since this only peaks some 12-24 months later, an "anabolic window" is created which results in a significant increase in bone mass, size and strength, as well as improvements in trabecular microarchitecture (Figure 8, p 137). PTH increases vertebral BMD by 10-15% over one to three years, and reduces the risk of new vertebral fractures by 60% and non-vertebral fractures by 50%, although separate data for hip fracture prevention are not available. The anti-fracture efficacy of PTH/teriparatide has also been documented in men and in subjects with GIOP.

Taking cognisance of costs, the availability of cheaper drugs and the need for daily injections, specific indications for the use of teriparatide/PTH have previously been recommended by NOFSA:

(i) Patients over age 65 years with a T–score ≤ -2.5 plus two or more fragility fractures, or multiple fractures and an uninterpretable DXA.

(ii) Failed treatment (> 12 months) with bone-active agents, as evidenced by the development of new fractures, or an unacceptable rate of bone loss on two or more consecutive follow-up BMD measurements.

(iii) Patients on chronic glucocorticoid therapy (three months or longer prednisone equivalent of ≥ 5 mg/day) with BMD ≤ -3.5, or ≤ -2.5 plus one or more fragility fracture, or multiple vertebral fractures.

The side-effects of PTH/teriparatide are usually limited to ***nausea***, ***headache*** and ***leg cramps***. ***Mild hypercalcaemia***, ***hypercalciuria*** and ***hyperuricaemia*** occur occasionally. Contraindications for the use of PTH/teriparatide have been established (Table XIII, p 140).

11.2.2 Fluoride

Although fluoride is a potent osteoblast mitogen which markedly increases BMD, its anti-fracture efficacy remains unclear. A recent meta-analysis suggested that fluoride significantly decreased vertebral and non-vertebral fractures when used in a daily dose

of ≤ 20 mg fluoride equivalents. Higher doses had no effect, or *increased* the risk of non-vertebral fractures.

11.2.3 NOFSA recommendations on the use of anabolic agents

NOFSA recommendations

a. ***Teriparatide,*** which is registered in South Africa, can be used in the treatment of osteoporosis, but only where specific indications exist (see 11.2.1, p 136) (GRADE 1/ØØØO).
b. Patients should be thoroughly assessed and contraindications (Table XIII, p 140) excluded. The *dose of teriparatide* is 20 µg/day, by subcutaneous injection, for 18 months. Serum calcium and uric acid should be monitored at one, six, and 12 months (GRADE 1/ØØØO).
c. *In patients taking hormone therapy (HT) or a selective estrogen receptor modulator (SERM),* teriparatide may be added to the existing treatment (GRADE 1/ØØOO). In those taking more potent antiresorptive agents (ARAs), like the bisphosphonates, it is less clear whether to switch to teriparatide (i.e. discontinue the bisphosphonate) or whether to add the teriparatide, although some evidence would favour the latter option (GRADE 2/ØOOO). Until fracture data become available, no firm recommendation on combination therapy can, however, be made.
d. Following *discontinuation of teriparatide*, BMD decreases rapidly and treatment with a bisphosphonate, strontium ranelate or a SERM is indicated to preserve bone mass gained (GRADE 1/ØØØO)
e. At present, we *cannot recommend that* ***fluoride*** *be used* in the treatment of osteoporosis (GRADE 1/ØØØO).

11.3 Drugs with dual or complex actions on bone

11.3.1 Strontium ranelate

Strontium ranelate is composed of two atoms of the non-radioactive trace element strontium and an organic moiety, ranelic acid. Preclinical studies suggest that strontium ranelate has a dual mode of action, resulting in the stimulation of bone formation and the inhibition of resorption. Animal studies have supported the in vitro data, although recent clinical studies have suggested that the drug has more complex actions.

Following strontium ranelate administration for three years, vertebral and hip BMD increase by 14% and 9%, respectively. The landmark SOTI and TROPOS trials documented that strontium ranelate reduced vertebral fractures by 40-50%, while hip fractures in women at high risk were reduced by 36%. These results have been confirmed in a placebo-controlled five-year extension

study, while an open–label extension study showed some evidence for sustained anti-fracture efficacy at eight years. Strontium ranelate is effective in subjects *over the age of 80 years*. Its anti-fracture efficacy has been proven in patients with osteoporosis, as well as in those with *osteopenia*. Strontium ranelate, which is a heavier element than calcium, is incorporated in bone and attenuates the penetration of X-rays through bone, and therefore results in an *overestimation of measured BMD*. This effect is maximal during the first year of strontium ranelate therapy, during which time it may account for up to 50% of the increase in BMD, continues to a lesser degree during the second and third year and, thereafter, the strontium ranelate content of bone reaches a plateau so that any further increase in BMD can be entirely ascribed to an increase in bone formation. *BMD monitoring* with strontium ranelate treatment is valuable, since it assesses both fracture risk reduction and treatment adherence.

Strontium ranelate is generally well tolerated. ***Nausea***, ***diarrhoea*** and ***headache*** are the most common adverse events reported, and usually subside within the first three months. The ***risk of VTE*** is thought to be marginally increased and a few cases of the ***DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome*** have been reported following treatment.

11.3.2 – 11.3.4 Vitamin D metabolites; anabolic steroids; diuretics

See the full guideline (p 147, 148) for details.

NOFSA recommendations

11.3.5 NOFSA recommendations on drugs with dual or complex actions on bone

a. ***Strontium ranelate*** should be regarded as *a first-line therapy* for postmenopausal osteoporosis. It is effective in those with osteoporosis as well as those with *osteopenia*, including the *very old (> 80 years)* (GRADE 1/ØØØO).

   Strontium ranelate should be taken on an empty stomach. It is best avoided in those with a *history of VTE* and should be discontinued if any significant *skin rash* develops within two to three months of initiating treatment (GRADE 1/ØØØO).

b. The ***vitamin D metabolites***, calcitriol and alfacalcidol, are *not recommended* for the treatment of osteoporosis (GRADE 1/ØØOO).

c. ***Anabolic steroids*** have a very small place in the treatment of osteoporosis. In the old, frail individual with advanced fracturing disease, a short course (e.g. six months) may be considered, largely to address sarcopenia (GRADE 2/ØOOO).

11.4 The choice of a pharmacological agent

Osteoporosis is not a single disease entity, but a heterogeneous syndrome, and very few head-to-head studies comparing the relative efficacy and safety of bone-active drugs have been published. Accordingly, *no ideal drug* can be recommended for the prevention and treatment of osteoporosis. The *choice* of a pharmacological agent will, therefore, largely *depend on:* (i) the disease profile (the osteoporosis syndrome), (ii) the patient profile, and (iii) available resources and personal preferences.

11.4.1 The disease profile (the osteoporosis syndrome)

- With very mild osteopenia without fractures or ongoing bone loss, lifestyle changes, with calcium and vitamin D supplementation, may suffice.
- With more significant osteopenia, consider hormone therapy (HT) or strontium ranelate.
- Give a bisphosphonate or strontium ranelate in subjects with DXA-confirmed osteoporosis (T-score $\leq$ -2.5).
- Reserve bone formation-stimulating agents for patients with severe osteoporosis, where mere maintenance of BMD is not sufficient.
- Consider skeletal sites involved; certain drugs (e.g. raloxifene) do not protect against non-vertebral fractures.
- Specific drugs may be indicated under certain circumstances (e.g. gonadal steroids in hypogonadism; additional vitamin D if accompanying osteomalacia is suspected).

11.4.2 The patient profile

- In the otherwise healthy subject merely requiring a bone-active drug, consider bisphosphonates or strontium ranelate.
- In the 50- to 60-year-old patient with menopausal symptoms, consider HT if it is not contraindicated.
- If the patient is at risk of breast cancer, consider a selective estrogen receptor modulator (SERM).
- In the frail, elderly patient with sarcopenia, also consider a short course of anabolic steroids.
- In men, young premenopausal women and children, consider referral to a specialist centre

11.4.3 Available resources and personal preferences

Given the lack of comparative data on efficacy and safety, drug selection should be individualised and an attempt should be made to always accommodate the preferences of the patient.

11.4.4 NOFSA recommendations on the choice of a pharmacological agent

a. We acknowledge the fact that, given the heterogeneity of the osteoporosis syndrome and the lack of significant head-to-head comparative studies, ***no ideal drug*** scenario can be recommended.

b. ***Drug therapy must be individualised,*** taking cognisance of the disease profile (particularly the severity of bone loss and skeletal sites involved), the patient profile (age, general health, concomitant disease, the clinical setting), and the available resources and personal preferences.

12. MONITORING OF THERAPY

Assessing the response to therapy is an essential part of managing osteoporosis.

NOFSA recommendations

12.5 NOFSA recommendations on the monitoring of therapy

a. Regular ***clinical assessment*** is essential to monitor disease progression, side-effects and adherence to therapy. Patient support programmes to improve understanding of the disease and, particularly, adherence to therapy are supported (GRADE 1/ØØØØ).

b. Since most vertebral fractures are asymptomatic, ***routine vertebral imaging*** (standard radiographs or DXA-based vertebral fracture assessment, DXA-VFA) is indicated every four to five years. Imaging is also indicated whenever a new vertebral fracture is suspected, e.g. back pain or loss of height (GRADE 1/ØØØO).

c. ***Routine BMD monitoring*** to assess the response to osteoporosis therapy has limitations, but is clinically useful if employed correctly (GRADE 1/ØØOO). Up to 75% of the fracture risk reduction following administration of anabolic agents and strontium ranelate is accounted for by changes in BMD. Regular BMD measurements are, therefore, invaluable to monitor fracture risk reduction and treatment adherence in these subjects. Monitoring the response to antiresorptive agents (ARAs) is more problematic, since a very poor correlation exists between BMD changes and the risk of vertebral fractures. Moreover, it has been suggested that up to 97% of patients in the FIT study responded to alendronate with an increase in hip BMD, which would question the need for routine monitoring. Other studies have, however, documented a reasonable correlation between changes in BMD and the risk of *non-vertebral fractures*. Further, not all studies have suggested a near-100% response to bisphosphonates, some reporting that up to 15% of patients do not respond. Even less favourable results

could be expected outside of an RCT, where it is known that 50% of patients on oral bisphosphonates do not adhere to therapy beyond one year. While there is no evidence to suggest that individuals whose BMD increased on treatment have better fracture protection than those whose BMD remained stable, there is evidence that those individuals whose BMD decreased progressively on therapy had higher fracture rates compared with those whose BMD increased or remained unchanged.

d. ***Only DXA should be used to follow up a patient's BMD.*** Diligent attention to *quality control* (including knowledge of the *CV (coefficient of variation) and LSC (least significant change)* of DXA machines used) is important. Follow-up measurements should always be made on the same instrument, using the "compare mode" or "copy mode" function. With few exceptions (e.g. glucocorticoid-induced osteoporosis, GIOP), a BMD measurement should *only be repeated after 18–24 months* of initiating therapy and not before that time (GRADE 1/ØØOO).

e. ***Interpret the first follow-up scan with caution***. An increase in, or unchanged, BMD, compared with baseline, should be used to motivate and improve patient adherence. A significant decrease in BMD should rarely, if ever, dictate an immediate change in therapy (although a further decrease on a subsequent DXA could), since it may still represent a favourable scenario (Figure 9, p 154), but should alert the care physician to the possibility of poor adherence or intercurrent disease/bone-toxic drugs (GRADE 2/ØOOO).

f. ***Bone turnover markers (BTMs)*** should not be used for *routine* monitoring, but may be employed in *problem cases* (e.g. to assess suspected poor adherence, treatment failure) (GRADE 1/ØØOO).

13. TREATMENT OF THE SYMPTOMATIC PATIENT

There is currently no consensus as to the best treatment of the acute, painful vertebral fracture, although traditionally this has been rather conservatively managed with analgesia, bed rest, physical support employing a brace or corset (short-term only), and subsequent gradual mobilisation. A role for the classical osteoporosis medications has been proposed by some, while others have recommended percutaneous vertebroplasty or kyphoplasty if pain does not rapidly subside.

NOFSA recommendations

13.6 NOFSA recommendations on treatment of the symptomatic patient

a. *The symptomatic acute vertebral fracture syndrome* must be treated with ***conventional analgesics***, supplemented with ***heat pads*** and ***ice packs*** (GRADE 1/ØØØO).

b. The use of ***physiotherapy, hydrotherapy, gradual mobilisation*** and ***back rehabilitation*** is important (GRADE 1/ØØOO).

c. Given the current state of our knowledge, the use of ***specific bone-active drugs***, like calcitonin, for the treatment of the symptomatic vertebral fracture syndrome does not appear to be cost-effective and cannot be recommended (GRADE 1/ØOOO).

d. Based on current medical evidence and, in particular, recently published randomised sham-operation controlled trials, the use of ***vertebroplasty*** cannot be recommended at present. We acknowledge that ***balloon kyphoplasty*** has the potential to partially restore the structural abnormalities that attend a vertebral fracture and has been shown, albeit in non-sham-operated subjects, to markedly relieve the pain of an acute vertebral fracture. Although evidence-based recommendations will have to await further studies, we suggest that balloon kyphoplasty be considered if severe back pain persists for six weeks following a vertebral fracture, particularly if the loss of vertebral height is no more than 50%, and STIR MRI (short TI inversion recovery magnetic resonance imaging) reveals the presence of bone oedema suggesting a recent fracture. Earlier intervention may be considered where the loss of height is more than 50%, whereas the absence of bone oedema on STIR MRI may suggest that a more conservative wait-and-see attitude be considered (GRADE 2/ØØOO).

FULL GUIDELINE

Abstract

***Objective**:* This document is an update of the clinical guideline published by the National Osteoporosis Foundation of South Africa (NOFSA) in 2000, which aims to improve the overall efficacy of the diagnosis and management of patients with, or at risk for, osteoporosis. The guideline is not limited to any particular patient group and targets all health care workers. A detailed summary, which is cross-referenced to the full guideline, is provided for the busy practitioner.

***Outcomes*:** The prevention of osteoporotic fractures and reduction in morbidity and mortality were the major considerations in the development of this guideline. Although no formal economic analysis was undertaken, the cost-efficacy of diagnostic and therapeutic interventions was considered in all recommendations.

Evidence: Systematic reviews and the highest level of evidence (randomised controlled trials (RCTs) and meta-analyses) were used as far as possible, and isolated descriptive studies and expert opinions were largely ignored. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria were used to describe the quality of evidence and the strength of recommendations. A draft guideline was developed, revised by the NOFSA Council during a two-day workshop, and finalised at a consensus meeting attended by relevant stakeholders.

***Key Recommendations**:* It is important to emphasise that this document should serve as a guide for clinical decision making and that it is not intended to represent rigid, prescriptive rules on patient management. The main recommendations are:

- Greater awareness about osteoporosis, its complications, prevention and treatment is necessary, as is broader access to health care for all patients suffering from this disease.

- Local research on the incidence of, risk factors for and normal reference data on osteoporosis is required. This will enable the formulation of a health economic strategy for the management of osteoporosis in this country.
- A diagnosis of osteoporosis is presently based on low bone mineral density (BMD) (a so-called T-score ≤ -2.5) or evidence of a fragility fracture.
- A BMD measurement should be performed in any patient if the indication, largely based on the patient's clinical risk factor (CRF) profile, is valid.
- BMD testing is indicated routinely in women over 65 years of age and in men aged 70 years and older.
- Central (axial) dual energy X-ray absorptiometry (DXA) should be used to measure BMD and to diagnose osteoporosis. Use the NHANES III young *female* reference data to determine T-scores in postmenopausal women and men older than 50 years of all races. Use Z-scores in younger individuals. A diagnosis of osteoporosis in children should be based on a low BMD (Z-score ≤ -2.0 corrected for body size, gender, ethnicity and pubertal status) *plus* a significant fracture history. Other techniques, including quantitative ultrasound (QUS), cannot be used to diagnose osteoporosis, but this does not preclude their use to assess fracture risk, particularly if axial (spine or hip) DXA is not available.
- The differences between *diagnostic criteria* and *interventional thresholds* are emphasised. The need to treat should not depend on a BMD value alone, but should also be determined by the patient's age (advanced age is the most important risk factor for osteoporosis, other than a low BMD), general health, willingness to consider treatment, the presence of prior fractures, CRFs and causes of ongoing bone loss, as well as the cost-efficacy and side-effects of available treatment.
- A thorough clinical assessment, BMD measurement employing DXA, search for evidence of vertebral fracture (using standard X-rays or DXA-based vertebral fracture assessment, DXA-VFA) and appropriate laboratory evaluation (to ensure that osteoporosis is the cause of the low BMD and not primary hyperparathyroidism or osteomalacia, and to exclude causes of secondary osteoporosis) are necessary before embarking on treatment with bone-active drugs.
- Initiate treatment in those with a BMD T-score ≤ -2.5 at the hip or lumbar spine.
- Initiate treatment in those with a typical osteoporotic fracture.
- Initiate treatment in postmenopausal women and in men with low bone mass or osteopenia (T-score between -1.0 and -2.5) in whom a clinical risk profile suggests above average risk of fracture. This might be assessed using the World Health Organization (WHO) FRAX® tool but, since little epidemiologic fracture data are available in this country, a simple algorithm (Figure 4, p 86) may be used in the interim.

- Non-pharmacological measures to improve bone strength and prevent falls are emphasised. Ensure an adequate intake of calcium (1,200mg per day) and vitamin D (800–1,000 IU per day; up to 2,000 IU per day during pregnancy and lactation); walk for 30-40 minutes, three times per week; employ simple clinical tools to assess and address the risk of falling; stop smoking; limit alcohol consumption to less than three drinks per day; and avoid bone-toxic drugs as far as possible.
- Osteoporosis is a heterogeneous syndrome and *no single ideal drug* can be recommended for treatment of all patients. The choice of drug should be individualised and is largely determined by (i) the *severity and nature of the disease* (e.g. non-pharmacological measures, calcium/vitamin D, and regular follow-up should suffice in those with very mild osteopenia and no fractures; consider hormone therapy (HT) or strontium ranelate for those with more significant osteopenia; a bisphosphonate or strontium ranelate for subjects with DXA-proven osteoporosis; and anabolic agents for those with advanced fracturing disease, an ultra-low BMD, or failed treatment with antiresorptive agents, ARAs); (ii) the *patient profile* (e.g. a bisphosphonate or strontium ranelate for otherwise healthy individuals with osteoporosis; HT for 50- to 60-year-old women with menopausal symptoms in whom HT is not contraindicated; a selective estrogen receptor modulator (SERM) for postmenopausal women with predominantly vertebral osteoporosis at risk of breast cancer); and (iii) *available resources* and *personal preferences*.
- Regular clinical, densitometric and morphometric (X-rays or VFA) monitoring is important. The clinician should be aware of the many pitfalls that exist in assessing the densitometric follow-up of patients, particularly those treated with ARAs.
- The acute painful vertebral syndrome should be treated with conventional analgesics, a short-term corset or brace, physiotherapy, hydrotherapy and gradual mobilisation. Given our current knowledge, the use of specific bone-active drugs (e.g. calcitonin) or vertebroplasty cannot, at present, be recommended for the treatment of the acute painful vertebral syndrome. Under certain circumstances, the use of balloon kyphoplasty may, however, be considered.
- Extensive dissemination of this guideline, including its electronic distribution, is necessary if key recommendations are to be implemented.
- The electronic version of the guideline, including its publication on the NOFSA (www.osteoporosis.org.za) and JEMDSA (www.jemdsa.co.za) websites, will allow for regular update.

1 Preamble and guideline objective

Osteoporosis is a *common* and *costly* disease which carries a *significant morbidity and mortality.*[1-11] The lifetime risk of a fracture in Caucasian women is 30-40%, and about 20% in men. The most common fractures are those of the vertebrae, proximal femur, distal radius and, to a lesser degree, the humerus, ribs and pelvis. However, most fractures in older subjects are due, in part, to low bone mass, even when they result from considerable trauma.[12-16] The annual cost of acute care of hip fractures in the USA exceeded $17 billion in 2005,[4] while osteoporotic fractures in Europe resulted in an estimated cost to the health services of around €30 billion in 2002.[14] After the age of 45 years, hip fractures in the UK, Europe and the USA account for a higher proportion of hospital bed occupancy than most other common disorders in women, including diabetes, coronary heart disease (CHD), obstructive airway disease and breast cancer.[17-19] Up to 20% of hip fracture victims die within one year of the event and more than 50% never regain the functional capability to lead an independent life. Vertebral fractures account for considerable morbidity and significant mortality, which have been shown to parallel that of hip fractures.[20,21]

In South Africa, the incidence of osteoporosis in our white, Asian (from the Indian sub-continent) and mixed-race populations appears to be similar to that of developed countries, although no fracture data exist. Like the USA, hip osteoporosis is less prevalent in our black populations, although vertebral bone mass, and possibly also vertebral fracture prevalence, in black and white South Africans appear to be similar. Further research on this important topic is clearly required.[22-24]

The National Osteoporosis Foundation of South Africa (NOFSA) published an Osteoporosis Clinical Guideline in 2000.[8] During the past decade, there have been enormous advances in our understanding of the disease, in our ability to identify those at risk of skeletal fracture, and in the proliferation of pharmacological agents that have been shown in randomised controlled trials (RCTs) to significantly reduce the risk of fracture. This document is an update of the original guideline, which aims to improve the efficacy and cost-effectiveness of diagnostic and therapeutic interventions for osteoporosis. Prevention of osteoporotic fractures and reduction in morbidity and mortality were the major considerations in the development of this guideline. Although no formal economic analysis was undertaken, the cost-efficacy of diagnostic and therapeutic interventions was considered in all recommendations.

The guideline is not limited to any particular patient group. Since primary osteoporosis more frequently affects postmenopausal females, this population is largely addressed, although younger females, men and children are also covered. All health care workers, the general practitioner, specialist and health authorities, are targeted by the guideline.

2 Methods of development

A draft guideline was compiled by the principal author, then debated and revised by the NOFSA Council during a two-day workshop, and finalised at a consensus meeting attended by all relevant stakeholders (Appendix I). To compile the guideline, systematic reviews and the highest level of evidence (RCTs, meta-analyses of RCTs and controlled studies) were used as far as possible, and isolated descriptive studies and expert opinions were largely ignored. Data sources consulted included electronic databases (e.g. MEDLINE, PubMed, Embase), systematic reviews (e.g. Cochrane Library) and handsearched journals, including recently published guidelines on osteoporosis. Due cognisance was, however, also taken of the limitations of controlled studies, including the fact that results from RCTs can usually not be widely extrapolated and can only be applied to specific populations and circumstances relevant to the study in question, as well as frequently overlooked differences in statistical vs. clinical significance, in relative and absolute risk, and in the way healthy controls and sick elderly subjects differ in their response to pharmaceutical interventions. Recommendations were formulated and final decisions were arrived at by formal consensus.

To describe the quality of evidence and the strength of recommendation, we primarily used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria.[25,26] GRADE uses four categories of quality: *High* (ØØØØ), where further research is unlikely to change our confidence in the estimate of effect; *Moderate* (ØØØO), where research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; *Low* (ØØOO), where research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and *Very Low* (ØOOO), where any estimate of effect is very unclear. The strength of recommendation was largely based on the quality of the evidence, although the magnitude of net benefit (benefit minus harm), cost-efficacy and availability issues were also considered. In accordance with GRADE, we used a score of 1 or *"we recommend"* for strong recommendations, and a score of 2 or *"we suggest"* for weak recommendations.

In addition to the GRADE criteria, we also employed the United States Preventive Services Task Force (USPSTF) methodology,[27] particularly to advise against an intervention or to indicate that no recommendation could be made. The USPSTF grades its recommendations (level A,B,C,D, or I) as follows: (A) *strongly recommends,* if evidence is good and benefits of intervention substantially outweigh harms; (B) *recommends,* if evidence is at least fair and

benefits outweigh harms; (C) *makes no recommendation,* if evidence is fair but the balance of benefits and harms is too close to justify a general recommendation; (D) *recommends against*, if good evidence exists that the intervention is ineffective or that harms outweigh benefits, and (I) *makes no recommendation because evidence is insufficient*, if evidence of efficacy is lacking or poor and balance of benefits and harms cannot be determined.

3 Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25OHD	25-hydroxyvitamin D
aBMD	areal bone mineral density
ABONE	Age BOdy size No Estrogen
AFF	atypical fragility fracture
ALP	alkaline phosphatase (total)
AMT	Abbreviated Mental Test
AP	anteroposterior
APOSS	Aberdeen Prospective Osteoporosis Screening Study
ARA	antiresorptive agent
ASBMR	American Society for Bone and Mineral Research
AST	alternate-step test
BA	bone area
BGP	bone Gla-protein (osteocalcin)
BMAD	bone mineral apparent density
BMC	bone mineral content
BMD	bone mineral density
BMD T-score	BMD value compared to that of the young adult reference mean
BMD Z-score	BMD value compared to age-, race- and gender-matched controls
BMI	body mass index
BMP	bone morphogenetic protein
BONE	IBandronate Osteoporosis vertebral fracture trial in North America and Europe
BRONJ	bisphosphonate-related osteonecrosis of the jaw
BSALP	bone-specific alkaline phosphatase
BTM	bone turnover marker

BUA	broadband ultrasound attenuation
CA2	carbonic anhydrase
CACS	coronary artery calcium stores
CaMos	Canadian Multicentre Osteoporosis Study
CaSR	calcium-sensing receptor
CE	conjugated equine estrogen
CHD	coronary heart disease
CI	confidence interval
CRF	clinical risk factor
CRP	C-reactive protein
CT	computed tomography
CTX	C-terminal telopeptides of D-Pyr
CV	coefficient of variation
DOES	Dubbo Osteoporosis Epidemiology Study
D-Pyr	deoxypyridinoline
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DVT	deep vein thrombosis
DXA	dual energy X-ray absorptiometry
eBMD	estimated bone mineral density
EMEA	European Medicines Agency
EPIDOS	EPIDemiology of Osteoporosis
EPISEM	combined EPIDOS and SEMOF cohorts
EPT	estrogen/progesterone therapy
ER	estrogen receptor
ESCEO	European Society for Economic Aspects of Osteoporosis and Osteoarthritis
ESR	erythrocyte sedimentation rate
ESR-1	estrogen receptor 1
ET	estrogen therapy
EUROFORS	European Study of Forsteo
EVOS	European Vertebral Osteoporosis Study
FACT	Fosamax Actonel Comparison Trial
FDA	Food and Drug Administration

FEA	finite element analysis
FIRST	Fracture International Run-in Strontium Ranelate Trial
FIT	Fracture Intervention Trial
FLEX	Fracture Intervention Trial Long Extension study
FPT	Fracture Prevention Trial
FRAX®	fracture risk assessment tool
FREE	Fracture Reduction Evaluation
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months
FSH	follicle-stimulating hormone
GIOP	glucocorticoid-induced osteoporosis
GLP	glucagon-like peptide
GR	gradient of risk
GRADE	Grading of Recommendation, Assessment, Development and Evaluation
HERS	Heart and Estrogen/Progestin Replacement Study
HIP	Hip Intervention Program
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
hPTH	recombinant human parathyroid hormone
HR	hazard ratio
HRCT	high resolution computed tomography
HRMRI	high resolution magnetic resonance imaging
HR-pQCT	high resolution peripheral quantitative computed tomography
HRT	hormone replacement therapy
HSA	hip structure analysis
HT	hormone therapy
ICTP	carboxyterminal telopeptides
IGF	insulin-like growth factor
IL-1	interleukin-1
IMS	International Menopause Society
INVEST	Investigational Vertebroplasty Efficacy and Safety Trial
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry

IVA	instant vertebral assessment
JEMDSA	Journal of Endocrinology, Metabolism and Diabetes of South Africa
LDL	low-density lipoprotein
LH	luteinising hormone
LIFT	Long Term Intervention on Fractures with Tibolone
LRP5	lipoprotein receptor-related protein 5
LSC	least significant change
LVA	lateral vertebral assessment (see VFA)
MAPK	mitogen-activated protein kinase
MHRA	Medicines and Healthcare products Regulatory Agency
MORE	Multiple Outcomes of Raloxifene Evaluation
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NaF	sodium fluoride
NETA	norethisterone acetate
NHANES III	Third National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NNT	number needed to treat
NOF	National Osteoporosis Foundation (USA)
NOFSA	National Osteoporosis Foundation of South Africa
NORA	National Osteoporosis Risk Assessment
NSAID	nonsteroidal anti-inflammatory drug
NTX	N-terminal telopeptides of D-Pyr
OFELY	Os des Femmes de Lyon
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
OPUS	Osteoporosis Prevention Using Soy
OR	odds ratio
ORAI	Osteoporosis Risk Assessment Instrument
OST	Osteoporosis Self-Assessment Tool
pDXA	peripheral dual energy X-ray absorptiometry
PEPI	Postmenopausal Estrogen/Progesterone Intervention
PICP	C-terminal propeptide of type 1 collagen

PINP	N-terminal propeptide of type 1 collagen
PMMA	polymethylmethacrylate
pQCT	peripheral quantitative computed tomography
PREVOS	PREVention Of early postmenopausal bone loss by Strontium ranelate
PROFET	Prevention of Falls in the Elderly Trial
PROOF	Prevent Recurrence of Osteoporotic Fractures
PRR	population relative risk
PTH	parathyroid hormone
PYR	pyridinoline
QUI	quantitative ultrasound index
QUS	quantitative ultrasound
QCT	quantitative computed tomography
RANK	receptor activator of nuclear factor-κβ
RANKL	RANK ligand
RCT	randomised controlled trial
RDA	recommended daily allowance
ROI	region of interest
RR	relative risk
RUTH	Raloxifene Use for The Heart (trial)
SARM	selective androgen receptor modulator
SCORE	Simple Calculated Osteoporosis Risk Estimation
SD	standard deviation
SEMOF	Swiss Evaluation of the Methods of measurement of Osteoporotic Fracture risk
SERM	selective estrogen receptor modulator
SI	stiffness index
SMWT	six-minute-walk test
SOF	Study of Osteoporotic Fractures
SOS	speed of sound
SOTI	Spinal Osteoporosis Therapeutic Intervention
SPA	single photon absorptiometry
SSBT	severely suppressed bone turnover
STEAR	selective tissue estrogen activity regulator

STIR MRI	short TI inversion recovery magnetic resonance imaging
STRATOS	STRontium Administration for Treatment of Osteoporosis
STS-5	sit-to-stand test with five repeats
SXA	single energy X-ray absorptiometry
TBLH	total body less the head
TENS	transcutaneous electrical nerve stimulation
TGF	transforming growth factor
TNF	tumour necrosis factor
TROPOS	TReatment Of Peripheral Osteoporosis Study
TSEC	tissue-selective estrogen complex
TSH	thyroid stimulating hormone
TUGT	Timed Up and Go Test (“get-up-and-go” test)
UCR	ultrasound critical angle reflectometry
USPSTF	United States Preventive Services Task Force
VERT	Vertebral Efficiency with Risedronate Therapy
VFA	vertebral fracture assessment (see LVA)
VIBE	EValuation of IBandronate Efficiency
vQCT	volumetric (3D) quantitative computed tomography
VTE	venous thromboembolism
WHI	Women’s Health Initiative
WHO	World Health Organization
µCT	micro-computed tomography

4 Definition of osteoporosis

4.1 The WHO and NIH definitions

Osteoporosis is currently defined by the World Health Organization (WHO) as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture, which usually involves the wrist, spine, hip, ribs, pelvis or humerus. The National Institutes of Health (NIH) define osteoporosis as a disease characterised by compromised bone strength predisposing to an increased risk of fracture.[1,2]

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 bone mineral content, BMC, or bone mineral density, BMD) currently embodies the practical basis for the diagnosis of osteoporosis. To the epidemiologist, a clinical outcome, such as a hip or vertebral fracture, is often included in the definition of osteoporosis. In 1994, the WHO proposed a stratified definition of osteoporosis,[2] which was updated in 2008,[3] encompassing the concepts of both low bone mass (BMC or BMD) and fracture. According to this classification, there are four general diagnostic categories (Table I).

Table I: World Health Organization classification of osteoporosis

Definition	Criteria[a]
Normal	BMD or BMC value (measured with DXA[b] at either the spine, total hip or femur neck) within 1 SD of the young adult reference mean (T-score[c] at or above -1.0)
Low bone mass	BMD or BMC value more than 1 SD, but less than 2.5 SD below the young adult mean (T-score between -1.0 and - 2.5)
Osteoporosis	BMD or BMC value is 2.5 SD or more below the young adult mean
Severe osteoporosis	BMD or BMC value more than 2.5 SD below the young adult mean, plus one or more fragility fractures

[a] These criteria were updated in 2008 and differ from those proposed by the WHO in 1994 by specifying a single reference site (the femoral neck) to measure BMD, providing a young normal reference range for women and men (the NHANES III reference data for femoral neck measurements in women aged 20-29 years), and by accommodating diagnostic criteria for men (see 6.2.1 and 6.3).
[b] DXA: dual energy X-ray absorptiometry
[c] When standard deviation (SD) units are used in relation to the young healthy adult population, this is referred to as the T-score.

4.2 Limitations of present definitions of osteoporosis

While the largely mass-based WHO classification has provided a practical basis for identifying the approximately 30% of postmenopausal Caucasian women 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 criterion:

- A single BMD measurement *lacks sensitivity*, since less than 50% of patients with a known osteoporotic fracture have a BMD value that is within the so-called osteoporosis range, i.e. T-score below -2.5.[28-31] Values for bone mass and for fracture risk are continuously distributed in the population, and a considerable overlap exists between BMD values in individuals with and without fracture. This is not surprising, given the fact that it is essentially a risk factor that is being detected and not a disease that is being diagnosed. A low BMD is no more than a *risk factor* which characterises the *disease* (osteoporosis), and predisposes to a clinical *complication* (fracture). Osteoporosis is, therefore, analogous to many other diseases (e.g. diabetes, hypertension) which are characterised by quantitative risk factors.
- BMD measurements are *quite specific* (85%) and generally regarded as useful surrogate markers of bone strength and fracture risk.[32,33] The mortality-adjusted lifetime risk of fracture for women with a T-score $\leq$ -2.5 is 65% (95% confidence interval, CI, 58–73%), and 42% for men (95% CI, 24–71%).[34] BMD measurements do, however, have limitations (see below) and circumstances are well documented where a high BMD does not necessarily translate into increased bone strength (e.g. high-dose fluoride exposure).[35]
- The WHO criteria are based on epidemiologic data obtained in healthy Caucasian postmenopausal women. Extrapolation of these criteria to *other populations, ethnic groups, young individuals and to males* should be discouraged. In men with large bones, the risk of fracture may be lower for equivalent T-scores, whereas fractures may occur at higher BMD values in, for example, glucocorticoid–induced osteoporosis (GIOP), where values ranging from 1.0[36] to 2.0[3] below the young mean have been suggested to identify those at risk of fracture.
- The WHO diagnostic criteria have largely been validated employing *dual energy X-ray absorptiometry (DXA)* of the axial skeleton (see below). There is, however, no general agreement at which *skeletal site(s)* to measure BMD, or which *reference data* to employ. Extrapolation of these criteria to other techniques (e.g. ultrasound, computed tomography) used to measure BMD, including the peripheral skeleton, may yield incorrect information regarding fracture risk. T-scores cannot, therefore, be used interchangeably between the different techniques available to measure BMD.
- *Bone quality* may significantly influence overall bone strength and is not considered in the WHO definition. Qualitative changes are more difficult to assess than BMD.

- While a low BMD is most commonly the result of osteoporosis, it may also occur secondary to *osteomalacia and primary hyperparathyroidism* or *combinations* of these so-called metabolic bone diseases. A definite diagnosis is essential for correct management, since osteomalacia and hyperparathyroidism are treated differently and are more amenable to therapy than advanced osteoporosis.
- The exclusively BMD-based diagnostic approach of the WHO classification does not include *extraskeletal risk factors,* like the propensity to fall. Patients with osteoporosis often have neuromuscular abnormalities, postural hypotension, poor vision, cognitive dysfunction or take drugs that predispose them to a fall.
- The four *diagnostic* categories developed by the WHO for postmenopausal Caucasian women cannot be employed as the only *therapeutic intervention thresholds* for all. The lack of sensitivity of BMD-based criteria on the one hand, and the emergence of largely BMD-independent risk factors to identify those at risk of a fracture on the other, has underscored the need for fracture risk assessment tools or algorithms to manage patients with osteoporosis.

In summary:

The limitations of BMD-based definitions of osteoporosis are the following:

A single BMD measurement lacks the sensitivity (± 50%) to identify those at risk of fracture.

BMD is a surrogate marker of bone strength and fracture risk.

The WHO criteria are based on data obtained from white postmenopausal women employing DXA of the axial skeleton, and cannot be extrapolated to other populations or techniques to measure BMD.

There is no general agreement on the skeletal sites which should be used to measure BMD, nor on the most appropriate reference data to use.

Bone quality is not assessed.

Extraskeletal risk factors are not addressed.

The causes of low BMD other than osteoporosis are not considered.

The WHO diagnostic categories cannot be employed as the only therapeutic intervention thresholds.

5 Determinants of skeletal strength and fracture risk

Cortical and trabecular bone tissue have three main constituents:

- Newly formed, unmineralised bone matrix (primarily structural type 1 collagen and a number of functional bone proteins, like osteocalcin).
- Bone mineral (hydroxyapatite crystals and amorphous calcium phosphate).
- Bone cells responsible for bone formation (osteoblasts) and bone resorption (osteoclasts), as well as those cells which control their adaptive and reparative remodelling (osteocytes).

In the normal adult, there is no short-term net gain or loss of skeletal mass, despite continuous bone remodelling (i.e. the maintenance-orientated turnover of bone which renews the skeleton and repairs micro-damage). This is accomplished by the tight *linking or coupling* of bone formation and resorption. Any uncoupling of this process will ultimately lead to a net gain or loss of bone mass. Throughout their lifetime, women lose about 10-30% of their cortical bone and 40-50% of their metabolically more active trabecular bone, whereas men lose about 50-60% of these amounts. Bone is lost in a biphasic pattern, with a slow age-dependent phase, occurring in both sexes, and a transient accelerated phase which occurs in women around the menopause (Figure 1).

5.1 Bone mass

Bone strength is largely determined by a combination of its mass and its qualitative properties. About 70% of bone strength in vitro is determined by the bone mass which, in turn, is a function of peak bone mass attained during early adulthood, age-related bone loss and total duration of loss. The fundamental pathogenetic mechanisms which underlie loss of bone mass and the development of osteoporosis, therefore, include (i) failure to achieve optimal peak bone mass, (ii) excessive bone resorption, resulting in loss of bone mass and disruption of architecture, and (iii) failure to adequately replace lost bone due to defects in bone formation.

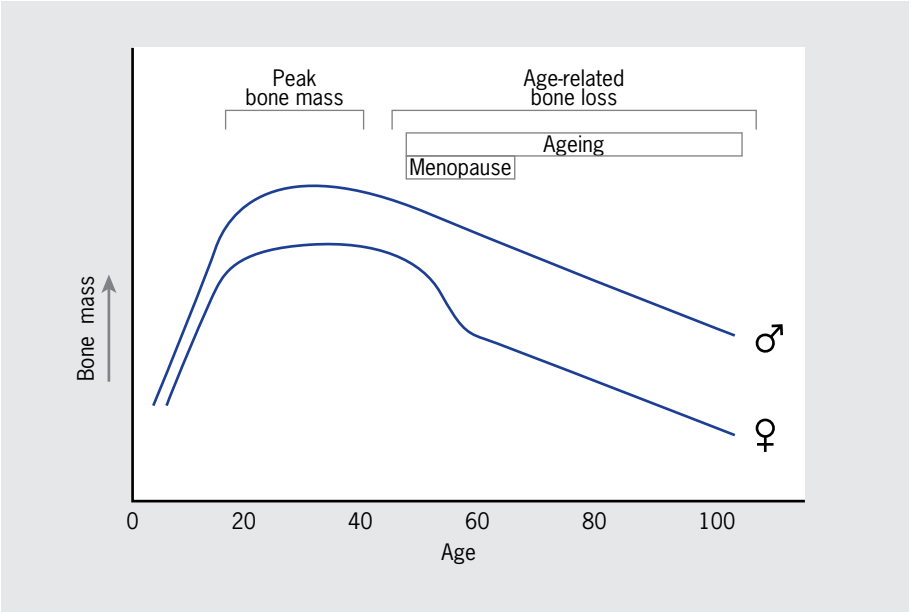


Figure 1: Changes in bone mass with age

5.1.1 Peak bone mass

Peak bone mass is mainly determined by heredity, body size and gender, although nutrition (particularly total energy and calcium intake), physical activity, normal pubertal development and good general health may exert a significant influence. More than 30 candidate genes (including those encoding the vitamin D receptor, parathyroid hormone (PTH) receptor, estrogen receptor, bone collagen, cytokines and bone matrix proteins like bone morphogenetic protein, BMP), have been linked to bone mass. Genetic factors also significantly influence bone size, bone quality and bone turnover.[37,38] Recently, polymorphisms in the genes encoding the estrogen receptor (ESR-1), the lipoprotein receptor-related protein (LRP5), the receptor activator of nuclear factor-κβ ligand (RANKL) and osteoprotegerin (OPG) were shown to be significantly associated with bone mineral density (BMD) and fracture risk in Caucasian women.[39-41] The recently published APOSS and OPUS studies have also documented associations between vitamin D polymorphisms and muscle power, balance and fall propensity.[42]

5.1.2 Age-related increased bone resorption

Age-related increases in bone resorption appear to result mainly from:

- Menopausal estrogen deficiency that results in increased osteoclastic bone resorption secondary to the elaboration of osteoclastogenic proinflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), which are negatively regulated by estrogen.[43,44]
- Estrogen-independent, age-related mechanisms, including secondary hyperparathyroidism caused by vitamin D deficiency,[45] poor calcium intake and/or impaired intestinal absorption of calcium.
- Additional factors are clearly operative (all women age and become estrogen deficient, yet not all develop osteoporosis), which may involve alterations in the RANK/RANKL/OPG system that regulates osteoclastogenesis or various cytokines, leukotrienes, prostaglandins and other systemic or locally produced bone-resorbing factors.[46]

5.1.3 Age-related impaired bone formation

The remodelling imbalance characterised by impaired bone formation that accompanies ageing may be due, in part, to osteoblast senescence and an age-related decrease in their capacity to replicate and differentiate. It also seems likely that defects in the production of local and systemic growth factors (e.g. BMP; insulin-like growth factor, IGF; transforming growth factor-beta, TGF-β), alterations in signalling pathways and transcription factors which regulate osteoblast differentiation and function (e.g. Wnt, LPR5, sclerostin), a decrease in physical activity, and reduced mechanical loading may contribute to the impaired bone formation.

5.1.4 Age-related (involutional) vs. pathological bone loss

If lifestyle factors (poor nutrition, lack of physical exercise, smoking, alcohol abuse), systemic disease, and/or the use of bone-toxic drugs (Table II) are superimposed on this age-related (involutional) bone loss, significant osteoporosis may ensue.

5.2 Bone quality

Bone strength is also influenced by qualitative structural and functional properties.

5.2.1 Macroarchitectural factors

Numerous studies have demonstrated that smaller bones are more prone to fracture than larger bones. Skeletal geometry, including the length and angle of the hip axis, also has

a significant bearing on bone strength. These factors may, in part, explain gender and population differences in fracture rates.

Table II: Risk factors for and causes of osteoporosis and fractures

Lifestyle factors[a]	
Alcohol (three or more drinks per day)[b]	Falling
Smoking[b]	High salt/protein intake
Low calcium intake	High caffeine intake
Inadequate physical activity	Excessive exercise
Immobilisation	Excess vitamin A
Vitamin D insufficiency	Vitamin C, K, B_6 and B_{12} deficiencies
Malnutrition	Trace element deficiencies
Low body mass (BMI < 20)[b]	
Genetic and ethnic factors	
Elderly females[b]	Porphyria
White, Asian and mixed race	Homocystinuria
Family history of hip fracture[b]	Idiopathic hypercalciuria
Osteogenesis imperfecta	Gaucher's disease
Marfan syndrome	Riley-Day syndrome
Ehlers-Danlos syndrome	Menkes disease
Haemochromatosis	
Diseases	
Hypogonadism	
Premature menopause	Turner's syndrome
Anorexia nervosa/bulimia	Klinefelter's syndrome
Athlete's amenorrhoea	Kallmann's syndrome
Delayed puberty	
Gastrointestinal disorders[c]	
Gastric bypass	Inflammatory bowel disease
Coeliac disease	Chronic liver disease
Gastrectomy	Pancreatic disease
Endocrinopathies[d]	
Cushing's syndrome	Acromegaly
Diabetes mellitus	Addison's disease
Hyperthyroidsim	Prolactinoma

Haematologic disorders	
Multiple myeloma	Leukaemia and lymphoma
Systemic mastocytosis	Sickle cell disease
Thalassaemia	Haemophilia
Rheumatology and immunology	
Rheumatoid arthritis[b]	Systemic lupus erythematosus
Psoriasis	Ankylosing spondylitis
Miscellaneous	
Alcoholism	Sarcoidosis
Malignancy	Post-transplant bone disease
Fracture after age 40 years[b]	Organ failure: lung, liver, kidney, heart
Parenteral nutrition	Pregnancy-associated osteoporosis
Amyloidosis	
Ageing factors	
Advanced age[b]	Secondary hyperparathyroidism
Qualitative factors	
Abnormal bone turnover	Small frame
Bone geometry	
Bone-toxic drugs	
See Table VII	
Risk factors for falls	
See Table VIII	

[a] Numerous "associated" and "risk" factors for osteoporosis have been proposed. Their relative importance as "causes" of osteoporosis clearly differ depending on age, gender, ethnicity, etc. In fact, the causal relationship between many of these conditions and the development of osteoporosis has not been conclusively verified in controlled studies.
[b] Risk factors included in the WHO FRAX® model (see Chapter 8).
[c] May also cause osteomalacia.
[d] Primary hyperparathyroidism is not a cause of osteoporosis.

5.2.2 Microarchitectural factors

Ageing is accompanied by increased *cortical* thinning and porosity. A decrease in *trabecular* size and number also occurs subsequent to impaired bone formation. Increased bone resorption causes a loss of trabecular connectivity, which results in an exponential decrease in bone strength with little, if any, change in bone mass.

5.2.3 Bone turnover

Bone turnover increases markedly around the menopause, following immobilisation, when the calcium balance is negative, and in certain diseases (e.g. hyperthyroidism, primary hyperparathyroidism). If bone turnover is increased, a proportionally larger amount of bone will be occupied by remodelling units and less by mineralised bone. Increased bone turnover will also increase the amount of unmineralised bone. Accelerated resorption may also perforate trabecular rods and plates. Increased bone turnover, therefore, not only decreases bone mass, but also causes qualitative structural defects in bone. It constitutes an important risk factor for fracture, independent of bone mass. Much less evidence is available as to the possible detrimental effects of a markedly suppressed bone turnover. This situation is encountered following long-term treatment with potent antiresorptive agents (ARAs) and will be discussed later.

5.2.4 Material properties of bone

These include complex processes like primary and secondary mineralisation, collagen composition and cross-linking, and micro-damage repair. The osteocyte has recently been identified as an important role player in the control of adaptive and reparative remodelling. Osteocyte numbers decrease with age, and even more so in those who fracture.[47]

5.3 Falls and fracture

If fragile bones are subjected to trauma, particularly those not protected by an adipose cushion, fractures may occur. An increased risk of trauma may result because of an increased propensity to fall and/or the loss of normal protective responses to a fall. Moreover, the frequency, severity and type of fall (e.g. sideways, forwards, backwards) appear to be important determinants of fracture risk (see 10.2).

In summary: The pathogenesis of the osteoporosis syndrome is complex and multifactorial. Bone mass is clearly the most important single determinant of bone strength, but qualitative factors and falls play a significant role in the development of fractures (Figure 2).

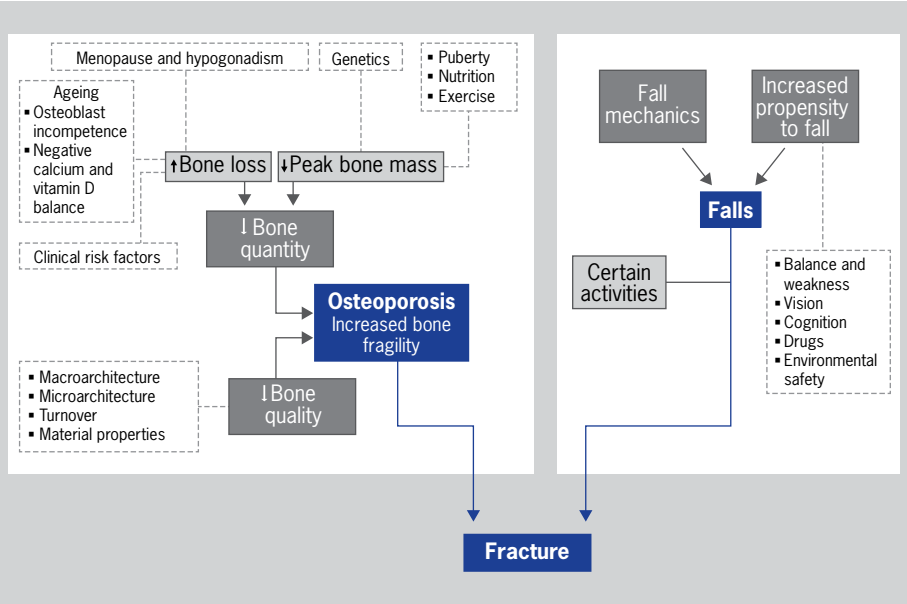


Figure 2: Pathogenesis of osteoporotic fracture

6 Diagnosis of osteoporosis

Currently, the diagnosis of osteoporosis is established by the measurement of *bone mineral density (BMD)*. A clinical diagnosis can also be made on the basis of a history or evidence of a *fragility fracture*.

6.1 Diagnostic techniques

A variety of techniques are available to measure bone mass, to detect osteoporotic fractures, and/or to assess bone strength and fracture risk. These include:

- Conventional skeletal radiology.
- Dual energy X-ray absorptiometry (DXA): vertebral fracture assessment (VFA) and hip structure analysis (HSA).
- Quantitative computed tomography (QCT) and high resolution CT (HRCT).
- Quantitative ultrasound (QUS).
- Tools to assess the peripheral skeleton (e.g. pQCT, pDXA).
- Other specialised techniques to assess bone density and/or structure.

6.1.1 Conventional skeletal radiology

Conventional radiography is employed to detect the presence of vertebral and appendicular fractures. Occasionally, typical pseudofractures regarded by most, although not all, as pathognomonic of osteomalacia[48] or areas of subperiosteal resorption suggestive of hyperparathyroidism are apparent. Conventional radiology of the spine, proximal hip and appendicular skeleton have also been used to detect low bone mass, but this is notoriously unreliable, since 30-40% of skeletal mass must be lost before osteopenia can be detected on routine radiographs. Moreover, some 25% of patients with apparent radiographic osteopenia (technical faults) or vertebral fracture (juvenile epiphysitis, trauma or even normal variations in vertebral body shape) have a normal BMD and may not be at increased risk of subsequent fractures.

Vertebral compression fractures are usually classified as wedge, central (concave or biconcave) or crush fractures. Crush deformities are thought to be indicative of more

severe osteoporosis. *A reduction in vertebral height of at least 20% or 4 mm is required for the diagnosis of a vertebral fracture.*[49] The semi-quantitative classification of vertebral fractures into Grade 1 or mild (20-25% reduction in height), Grade 2 or moderate (25-40% reduction in height) and Grade 3 or severe (> 40% reduction in height) proposed by Genant et al[50] many years ago is still regarded as the gold standard. The presence of a prevalent vertebral fracture is an important risk factor and increases the likelihood of subsequent vertebral fractures two- to 10-fold.[51,52] Fractures resulting from osteoporosis are usually anteriorly wedged. High thoracic (above T4) or posteriorly wedged (other than L4 and L5) fractures should suggest the possibility of a cause other than osteoporosis. These include neoplastic diseases like multiple myeloma and malignant metastases, osteomalacia, juvenile epiphysitis (Scheuermann's disease), trauma and degenerative abnormalities.

6.1.2 Dual energy X-ray absorptiometry

6.1.2.1 Use of DXA to measure BMD

DXA measures the attenuation of X-rays of two different photon energies that are passed through the body, allowing for the measurement of bone and soft tissue mass. The machine computes the bone mineral content (BMC in g) and areal bone mineral density (aBMD in g/cm^2) for a given region of interest (ROI).

DXA is capable of measuring the bone mass of the lumbar vertebrae, various hip areas and the distal radius, as well as the total body, *very accurately* (4-8% error), *precisely* (1-3%) and *safely,* with negligible radiation exposure. The WHO diagnostic criteria (Table I) are based on the use of central DXA, and numerous studies have underscored its value in assessing fracture risk.[53-58] Its ease of use and short measurement times are further advantages. DXA is also well established in South Africa, with both state and private patients having ready access to this commodity.

A number of *limitations* of DXA should, however, be recognised:

- DXA measurements are two-dimensional, providing an *areal* BMD, as opposed to a true three-dimensional *volumetric* bone density. Larger bones may, therefore, have higher BMD values than smaller bones, even when no true difference in density exists. Attempts have been made to correct for body (bone) size and to calculate a volumetric density by using formulae like the bone mineral apparent density (BMAD = BMD/$\sqrt{BA}$, where BA=bone area).[5,60] This technique has, however, largely remained a research tool.
- DXA cannot distinguish between cortical and trabecular bone.
- The establishment of appropriate local reference values for BMD is very important. Reference data supplied by overseas manufacturers are often not appropriate for our heterogeneous local populations (see below).

- Degenerative disorders, aortic and other vascular calcifications, and previous contrast media, fractures or deformities may complicate (falsely elevate BMD) and even invalidate interpretation of spine scans, particularly in the elderly. Variable soft tissue density may be the source of errors, particularly non-uniformly distributed fat in the lumbar region and within the vertebral bone marrow, which will result in an underestimation of BMD.
- Operator errors may occur. Although DXA is very user-friendly, thorough initial densitometry training and regular updates are important. NOFSA is affiliated with the International Society for Clinical Densitometry (ISCD) and regularly holds training courses for both DXA operators and physicians. Regular evaluation of accuracy (at least weekly scanning of phantoms and plotting of BMD measurements) as well as precision (regular measurement of patients to determine the coefficient of variation, CV, and least significant change, LSC) is an essential part of the quality control of any patient care practice, and should not be regarded as research.

6.1.2.2 Use of DXA to detect fractures (VFA)

DXA can also be employed to *visualise* the lateral spine, from approximately T4 to L5, to detect vertebral fractures.This should not be confused with *measuring the BMD* of the lateral spine, which is not recommended for routine clinical use. A prior fracture after the age of 50 years is regarded as one of the most important clinical risk factors (CRFs), increasing the risk of future fractures on average fivefold. Moreover, since up to 60% of vertebral fractures are asymptomatic, they are often missed if not routinely searched for. Whereas lateral X-ray of the spine remains the gold standard for vertebral fracture detection, this is often only requested when a fracture is suspected and may require referral to a different facility. Newer DXA systems are equipped with *VFA software* (previously called lateral or instant vertebral assessment, LVA/IVA), which allows for convenient, point-of-care examination at a lower radiation dose and cost than conventional spine X-rays.[61,62]

The ISCD recommends that the Genant visual method be used to diagnose vertebral fracture, since the semi-automated morphometry methodology alone is unreliable.[32] Although image resolution is lower than with standard X-rays, VFA has a sensitivity and specificity of around 90% for the detection of grade 2 and grade 3 fractures[4] and an overall sensitivity of 68%, which underscores the fact that this technique can adequately detect significant vertebral fractures, but is a rather poor method with which to identify grade 1 lesions.[62,63] Approximately 97% of vertebral bodies can be analysed, up to T7.

The ISCD has published a number of *indications for VFA,* which largely include subjects with osteopenia, plus a possible vertebral fracture, advanced age or a secondary cause of osteoporosis.[32] Patients with osteoporosis are also included if documentation of vertebral fractures “will alter clinical management”. Given the fact that vertebral fractures often occur asymptomatically, periodic screening for new spine fractures should be performed

routinely. It seems reasonable to include a thorough baseline spine assessment, employing either standard X-rays or VFA, in the initial evaluation of not only osteopenic patients, but also those with DXA-confirmed osteoporosis.[61]

6.1.2.3 Use of DXA to assess bone structure (HSA)

HSA software is now provided by several DXA manufacturers, and can be used to assess hip geometry and mechanical properties. This modality has yielded novel information on how fracture risk is affected by exercise and various bone-active drugs.[64,65]

6.1.3 Quantitative computed tomography

6.1.3.1 Use of QCT to measure BMD

QCT measures true volumetric density (g/cm^3), rather than areal density (g/cm^2), of the spine, which is independent of bone size. It can also discriminate between the metabolically more active trabecular and less active cortical bone of the spine, which suggests that this technique may be more accurate in assessing early bone loss.[66] Compared with DXA, the higher precision error, radiation dose (50-100 uSv) and cost make this technique less ideal for patient follow-up.[67] Numerous cross-sectional studies have shown a relationship between fracture risk and QCT bone density in postmenopausal women (little data are available in men), but few studies have demonstrated the utility of QCT to predict fracture risk prospectively.[68,69] Several large cohorts have recently included QCT measurements, and these data are being awaited.

6.1.3.2 New QCT techniques to assess bone structure

QCT-based techniques have been used to assess vertebral and femoral geometry, while high resolution multislice spiral CT (HRCT), which images vertebral trabecular architecture, is said to provide superior discrimination of those at risk of fracture.

6.1.4 Quantitative ultrasound

A number of ultrasound variables have been employed to assess bone density (± structure) and include (i) velocity (e.g. speed of sound, SOS), (ii) attenuation (e.g. broadband ultrasound attenuation, BUA), and (iii) reflection (e.g. ultrasound critical angle reflectometry, UCR). QUS can be performed at the heel, tibia, patella and other peripheral skeletal sites. The ISCD only recommends measurements at the heel.

These variables, either alone or in combination, have been shown to predict fracture risk in both cross-sectional and longitudinal studies.[70-72] Controversy still exists as to whether QUS parameters merely reflect bone mass, or whether they also provide insights into the quality

of bone. The ISCD states that heel QUS has been validated to predict hip and vertebral fractures in postmenopausal women and in men over the age of 65 years, independently of central DXA BMD.[32]

Most studies suggest that measurements of BUA and SOS at the heel are associated with a 1.5- to 2-fold increase in fracture risk for each standard deviation (SD) decrease in BMD. Ultrasound is less expensive than densitometry, measuring time is short, and the device is portable and uses no radiation source.

6.1.5 Measurement of the peripheral skeleton

Single photon absorptiometry (SPA) and single energy X-ray absorptiometry (SXA) are outdated techniques seldom used today. Recently, the use of peripheral DXA (pDXA), peripheral quantitative computed tomography (pQCT), radiographic absorptiometry of the hand and techniques to measure phalangeal mineral density have gained in popularity. These techniques are cheap and are likely to become widely accessible in this country in the near future. They require careful quality control, can be used to assess appendicular sites and cannot measure the clinically more important axial BMD of the spine or hip.

More recently, high resolution peripheral computed tomography (HR-pQCT) has been introduced to evaluate the trabecular and cortical microarchitecture and density of the distal radius and tibia. This technique possesses excellent precision for both density (< 2%) and structure (< 4%) measurements, and some data on fracture discrimination are also very promising. Data on treatment intervention studies are, however, being awaited.[73,74]

6.1.6 Other specialised techniques to assess bone structure

A number of new techniques, including three-dimensional volumetric quantitative CT (vQCT), micro-CT (μCT), high resolution magnetic resonance imaging (HRMRI), micro-MRI (μMRI), and QCT-based finite element analysis (FEA), are currently being tested to assess structural bone properties, but are not yet available for clinical use.

6.2 Clinical application of bone mass measurement

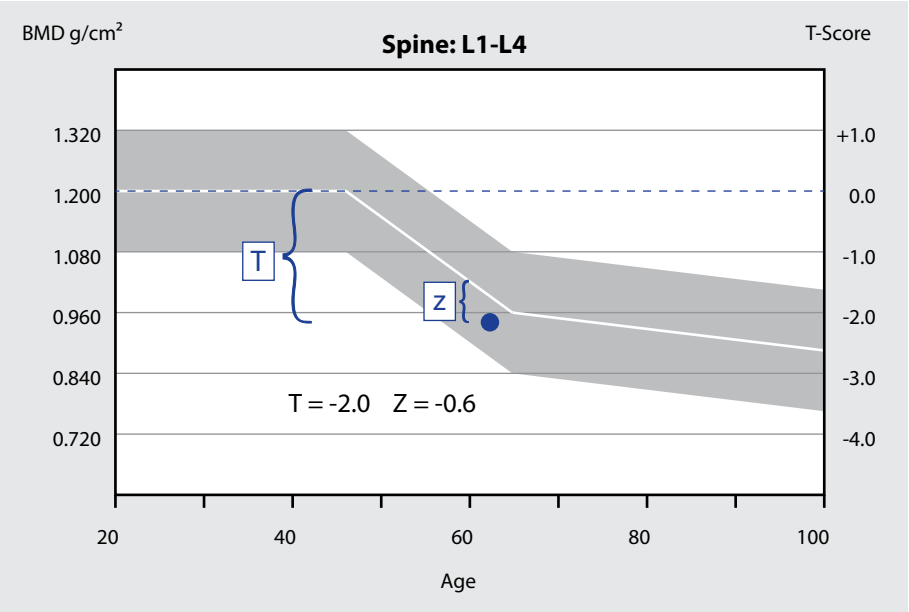
Bone mass measurements are largely employed to make a diagnosis of osteoporosis and to aid in the decision whether or not to initiate treatment with a bone-active agent. There is a limited place for BMD measurement in therapeutic decision making and in patient follow-up.

6.2.1 To diagnose osteoporosis

The original WHO criteria for the diagnostic interpretation of bone mass data in postmenopausal females (Table I), as well as the limitations (see 4.2), have been alluded to.

Figure 3 emphasises the difference between a T-score (the individual's BMD compared with that of the young, adult reference mean), and a Z-score (compared with age-, gender- and race-matched controls).

The 1994 WHO criteria employed only DXA, and provided for diagnosis of osteoporosis at the hip (total or neck) and anteroposterior (AP) spine or forearm.[2] Currently, the ISCD recommends DXA measurement at the hip (using the lowest value of the femur neck or total hip) or spine (L1-L4; exclude a vertebra if it differs by more than 1.0 T-score from an adjacent vertebra; diagnosis must be made on a minimum of two vertebrae). The distal (one-third) radius can be used if the hip or spine cannot be measured or interpreted. A diagnosis of osteoporosis is based on the lowest of these values. The new WHO/IOF guidance[3] specifies a single reference site to diagnose osteoporosis, namely the femoral neck. In 2008, the American NOF[4] recommended measurement at the femoral neck and the spine.



Adapted from ISCD official positions, 2007[32]

Figure 3: Schematic presentation: 60-year-old woman with a BMD of 0.958 g/cm², which relates to a T-score of -2.0 and a Z-score of -0.6 on this particular DXA machine

There appears to be general agreement that the NHANES III reference database for young Caucasian women be used to determine T-scores in postmenopausal women.[3,4,32] The most appropriate use of T-scores for men over the age of 50 years, however, remains controversial. The ISCD recommends the use of a male reference database, the new WHO/IOF uses a single reference population (the NHANES III *female* Caucasian database for assessing fracture risk in both genders), while the American NOF has called for more research. For premenopausal women, men younger than 50 years of age and children, the WHO BMD criteria and use of T-scores should not be applied. Instead, the age-, gender- and race-corrected values, or so-called Z–scores (Figure 3), are recommended. A Z-score below -2.0 is regarded as abnormal and should be referred to as "low BMD for age".

Diagnosis of osteoporosis in children. There is consensus[75,76] that the *diagnosis of osteoporosis in children* should NOT be made on the basis of a BMD measurement alone, but requires both (i) a clinically significant fracture history (i.e. one long bone fracture of the lower extremities, or two or more long bone fractures of the upper limbs, or a vertebral compression fracture), and (ii) a BMD or BMC Z-score $\leq$ -2.0 adjusted for age, gender and race, as well as for body size and pubertal development (Tanner stage). T-scores are, of course, never applied to children. The ISCD recommends that BMD should be measured employing DXA, and that the lumbar spine and the total body less the head (TBLH) are the preferred sites.[32]

6.2.2 To assess fracture risk and aid in therapeutic decision making

An increase in fracture risk with diminishing bone mass is firmly established, with the gradient of risk (GR) lying between 1.5 and 3.0 for each SD decrease in BMD for most of the devices employed to measure bone mass.[53-55] DXA, as well as QUS, QCT and the peripheral devices, have been shown to be useful in predicting fracture risk. A single BMD measurement, however, lacks the sensitivity to adequately identify those at risk of a fracture. This can be improved by:

- *Site-specific measurements*. BMD measurements at different anatomical sites are usually significantly correlated (r = 0.4-0.8) in healthy populations. In individual subjects, particularly the elderly and those with osteoporosis, this correlation becomes less impressive.[53-56,77-79] There is little doubt that a BMD measurement at any specific skeletal site is the best predictor of fracture at that site. For example, the age-adjusted relative risk (RR) of hip fractures for each SD decrease in BMD is twofold higher for measurements of the hip than for assessment of BMD at spine or appendicular sites.
- *Combining a bone mass measurement* with assessment of clinical (Table II), radiological (presence of fractures), biochemical (bone turnover) and, possibly, other (QUS, genotyping) risk factors (see below).

6.2.3 To assess the severity of osteoporosis and rationalise the type of therapy

To date, BMD data have generally had little influence on the specific drugs used to treat osteoporosis. Although bisphosphonates have been shown to be effective in patients selected solely on the basis of prior vertebral[80] or hip[81] fractures, the HIP study[82,83] revealed that risedronate was ineffective in preventing fracture in elderly women with a BMD T-score above -2.5, suggesting that alternative therapeutic strategies may have to be considered in those with CRFs and less severe bone loss. Conversely, an extremely low BMD (e.g. T-score -4.0) may argue against treatment with antiresorptive agents (ARAs) alone, which only modestly increase BMD and, instead, suggest the use of an anabolic agent. Assessment of severity and site(s) of bone loss may, therefore, assist in the rational choice of therapy.

6.2.4 To assess rate of bone loss in untreated subjects

Not infrequently, the indications for pharmacological intervention in a particular subject are not clear and a decision is made to follow up the patient conservatively. Periodic assessment of BMD may then be required.

The probability of detecting a difference in BMD between two measurements depends on the following:

- Precision of the technique.
- Rate of bone loss at a particular site.
- Follow-up time between measurements.

Currently, DXA has the lowest precision error (1-3%) and is regarded as the preferred technique to assess the rate of bone loss or gain. QCT and QUS are less precise and not recommended for follow-up.[3,4,6,32,66-69] The rate of postmenopausal bone loss ranges from < 1% to > 5% annually, suggesting that subpopulations of fast and slow bone losers may exist.[84,85] The average rate of postmenopausal loss is, however, 1-2% per year. Since this is of the same order as the precision of DXA, the minimum duration of follow-up needed to detect a significant difference using this device is 18–24 months. Earlier follow-up (e.g. six to 12 months) may, however, be indicated for conditions characterised by rapid initial bone loss, e.g. glucocorticoid- or aromatase inhibitor-induced osteoporosis.

6.2.5 To monitor the response to therapy

Changes in BMD, following initiation of treatment with ARAs, account for less than 20% of the variance in fracture risk reduction. Other than detecting an unexpected marked decrease in BMD, monitoring is of limited value in subjects treated with ARAs. Drugs with

anabolic actions like teriparatide and strontium ranelate, however, significantly increase BMD, and use of BMD monitoring under these circumstances may be more useful.[86]

6.2.6 To improve compliance and persistence

There is little evidence that compliance can be improved with reinforcement in subjects who have already sustained a fracture. However, in those who have no history of fracture, reinforcement strategies using BMD[87,88] and bone marker data[89] do suggest that adherence might be improved.

6.3 NOFSA recommendations on the diagnosis of osteoporosis

NOFSA recommendations

a. ***Confirm the diagnosis before initiating treatment.*** We recommend that a diagnosis of osteoporosis, based on a bone mass measurement or evidence of fragility fracture, be made prior to the initiation of long-term therapy, the monitoring of which is often difficult. BMD measurements allow for assessment of the severity of the disease and the site(s) of involvement, and may also impact on the type of therapy selected, patient motivation and follow up. Moreover, the efficacy of pharmacological intervention has largely been demonstrated in patients with a low BMD, in subjects with a prior fracture, and in those on chronic glucocorticoids.[80,81] The efficacy of bone-active drugs in preventing fractures in patients with other risk factors, therefore, remains largely unknown (GRADE 1/ØØOO).

b. ***Use DXA to measure BMD.*** We recommend that, given its accuracy, precision, low radiation dose, short scanning time, ability to predict fracture and validation in the WHO classification of osteoporosis, central (axial) DXA be used to assess BMD and to diagnose osteoporosis. It is also the technique of choice to assess rates of bone loss or gain. We do not recommend the use of other techniques, including ***quantitative CT (QCT)*** and ***quantitative ultrasound (QUS)***, for the diagnosis of osteoporosis (USPSTF D/ØØØO). This does not preclude their use to assess fracture risk, particularly if central DXA is not available (see 6.2.3 and 6.2.4). These techniques are not suitable for patient follow-up. Furthermore, results from these technologies should be interpreted with caution and, in particular, cannot be applied to the T-score-based WHO diagnostic classification of osteoporosis (GRADE 1/ØØØO). We take cognisance of the development of new technologies to assess not only bone mass, but also bone structure and quality, and acknowledge their potential role in the future management of patients with osteoporosis, but cannot make a recommendation about their use at present (USPSTF I/ØOOO).

c. ***Selection of skeletal site(s).*** We cannot make an evidence-based recommendation on the skeletal sites at which a BMD should be measured

NOFSA recommendations

(USPSTF I/ØOOO). Measurement at the metabolically more active spine has the advantage of identifying changes in BMD earlier, although degenerative changes may cause false negative results, particularly in the elderly. In both women and men, lumbar spine BMD is only weakly associated with the risk of hip fracture.[90,91] The new WHO/European guidance recommends measurement at a single site, the femoral neck, and argues that prediction of fracture is not improved by the use of multiple sites.[92,93] The American NOF advocates measurement at the spine or the femoral neck. For the sake of uniformity, we suggest that the recommendations of the ISCD,[32,94,95] to use BMD values at the spine, femur neck and total femur (or distal radius if measurements at the spine and hip are invalid), be used (see 6.1.2.1.) (GRADE 2/ØOOO).

d. ***Interpretation of BMD results.*** A diagnosis of osteoporosis is based on the lowest BMD value obtained. BMD results in ***Caucasian postmenopausal women*** should be expressed as T-scores employing the WHO criteria (Table I) and the NHANES III reference databank, while Z-scores should be used in ***premenopausal women*** and ***men under 50 years of age*** (GRADE 1/ØØØO).

e. ***Diagnosis of osteoporosis in men.*** No evidence-based recommendations on the interpretation of BMD data in ***men over the age of 50 years*** can be made (see 6.1.2.1) (USPSTF I/ØOOO). It is well documented that, in men, the risk of fracture is substantially lower for BMD within their own reference range.[96] It would, therefore, seem reasonable to employ more stringent criteria to yield the same fracture risk as in women. Two approaches have been proposed in this regard. One involves the use of a lower absolute value of BMD as a cut-off in men (e.g. that used in females), while the other suggests different diagnostic criteria (e.g. using a T-score of -3.0, instead of -2.5, to diagnose osteoporosis). The new WHO/European guidance has opted for the former, and uses the same absolute threshold in both men and women.[3] It is suggested that the new WHO/European recommendation, to employ female reference data to determine T-scores in males over the age of 50 years, be used (GRADE 2/ØOOO).

f. ***Diagnosis of osteoporosis in black populations.*** The need to develop local BMD reference values in different populations is apparent. Mean BMD values in South African black populations[23,24] appear to be lower than those of African Americans used by the DXA manufacturers. Until local reference data become available, it is suggested that reference data for Caucasian females be used for subjects of all races (GRADE 2/ØOOO).

g. ***Diagnosis of osteoporosis in children*** (see 6.2.1) should be based on a low BMD (Z-score < -2.0) after adjustment for body size, ethnicity, gender

and pubertal status (Tanner stage), plus a significant fracture history (GRADE 1/ØØØO).

h. ***Indications for bone mass measurement.*** We recommend that BMD be performed based on specific indications, as opposed to unselected screening (GRADE 1/ØØØO). There is general agreement that the argument for screening all women is poor.[3,5,6,8,32] Numerous risk assessment instruments have been developed to identify individuals in whom a BMD measurement is indicated. One, the Osteoporosis Risk Assessment Instrument (ORAI),[97,98] includes age, body mass, and current estrogen use. The Age BOdy size No Estrogen (ABONE) is a similar, but simpler, instrument that uses the same variables.[99] The Simple Calculated Osteoporosis Risk Estimation (SCORE)[100] is based on race, the presence of rheumatoid arthritis, low trauma fracture, estrogen use, age and weight, while the Osteoporosis Self-Assessment Tool (OST)[101] includes only age and body weight. The relative importance of these risk factors does, however, depend on the local population, age, gender and general health. For example, a recent extensive systematic review of the literature concluded that, in healthy 40- to 60-year-old women, only a low body weight and menopausal status can be considered as important risk factors for low BMD,[102] while a local survey cautioned that conventional clinical risk factors (CRFs) in Caucasians may not be relevant in our black populations.[24] Our current recommendations (Table III) are adapted from previous NOFSA guidelines,[8,103] with the single important change being the inclusion of *age* as an independent indication in the current recommendations. Both the American NOF,[4] as well as the ISCD,[32] include women aged 65 years and older and men over the age of 70, regardless of any other CRF (GRADE 1/ØØOO). In children, it is suggested that DXA be limited to those with (i) a significant fracture history, (ii) diseases associated with known bone loss (e.g. requiring the use of glucocorticoids), and (iii) for follow-up purposes (GRADE 2/ØOOO).

i. ***When to test.*** We recommend that an initial BMD measurement is acceptable at any time if the indication is valid. Given the precision errors (1-3%) of current DXA devices, it is recommended that routine follow-up scans be performed every 18-24 months, although earlier assessment may be indicated for conditions characterised by rapid initial bone loss, e.g. glucocorticoid-induced osteoporosis (GIOP) (GRADE 1/ØØØO).

j. ***Routine vertebral fracture assessment (VFA).*** We recommend that evidence (clinical and morphometric) of fracture be sought in all patients who qualify for a bone mass measurement. Standard X-rays or DXA-based VFA technology can be employed for this purpose (GRADE 1/ØØOO). The Genant

semi-quantitative system (Grade 1 – 3) should be used to classify fractures (GRADE 1/ØØØO).

Table III: Indications for bone mass measurement

1. Women aged 65 years and older, and men over the age of 70 years.
2. Known causes of secondary osteoporosis:
   - Early menopause (< 45 years of age), prolonged (longer than one year) oligo- or amenorrhoea in premenopausal women, or other causes of hypogonadism in women or men.
   - Systemic diseases known to adversely affect bone (Table II).
   - Bone-toxic drugs (Table VII).
3. Radiographic evidence of vertebral fracture or apparent osteopenia.
4. History of fragility fracture after age 40 years.
5. Presence of strong clinical risk factors:
   - Family history of hip fracture or osteoporosis.
   - Excessive leanness (BMI < 19 kg/m^2).
   - Regular alcohol intake (three or more drinks per day).
   - Smoking.
   - Poor nutrition/calcium intake/Vitamin D exposure.
6. To facilitate decisions regarding drug initiation or discontinuation (e.g. hormone therapy, bisphosphonates).

7 Fracture risk assessment

Studies have shown that less than 50% of women with an osteoporotic fracture have a bone mineral density (BMD) value within the so-called osteoporosis range (i.e. T-score below -2.5), and that most fractures (± 60%) occur in those with osteopenia (T-score -1.0 to -2.5).[18,28-31,104-107] The sensitivity to identify fracture risk can be increased by lowering the BMD threshold to a T-score of, for example, -2.0, but this would significantly decrease the specificity of the test.[107] A better alternative to improve the gradient of risk (GR) is to combine the BMD measurement with other risk factors. These could include one or more of the following:

- Clinical risk factors (CRFs).
- Assessment of bone turnover (biochemistry, bone histology).
- Other risk factors (quantitative ultrasound, QUS; genetic markers).

7.1 Clinical risk factors

Numerous CRFs for osteoporosis have been identified, some of which are listed in Table II. CRFs have been used (i) to identify those at risk of fracture who may be appropriate for BMD testing, (ii) in combination with BMD (as well as biomarkers and ultrasound), to assess fracture risk and to help choose which patients to treat with bone-active drugs, and (iii) in those situations where BMD is not available, to select patients in whom treatment should be considered. As a rule, CRFs lack sensitivity and tend to differ amongst patient populations. They do, however, impact on each other and are *additive in predicting fracture*.

Employing meta-analyses from large prospective population studies, a number of major CRFs have recently been identified.[3,4,7,108-111] One such meta-analysis of nine population-based studies, involving more than 46,000 subjects, concluded that CRFs alone predicted hip fracture at age 50 years with a GR of 2.1/SD. The use of BMD alone provided a higher GR (3.7/SD), which was improved further with the combined use of CRFs and BMD (4.2/SD).[112]

7.1.1 Age

Age is a major predictor of fracture, surpassed only by a BMD measurement in the osteoporosis range. Risk is independent of bone mass and, for any BMD, fracture risk is two- to fivefold higher in the elderly than in the young.[34,113-115]

7.1.2 Gender and ethnicity

Osteoporosis occurs more frequently in women than in men. This difference is partly due to a greater bone size and, thus, higher areal BMD in men, but also involves a less abrupt decline in gonadal function with ageing (with its accompanying microarchitectural deterioration), larger muscle mass and shorter life expectancy.

The incidences of osteoporosis and fractures vary markedly between different races and populations. In South Africa, the incidence of osteoporosis in our white, Asian and mixed-race populations appear to be similar to that of developed countries, but no accurate fracture data exist. This is important because, even within the relatively homogeneous populations of Europe, fracture risk differs up to 10-fold between countries.[3,6] The significantly lower incidence of osteoporosis in black, compared with white, Americans is largely explained on the basis of a higher average BMD in the former. As in the USA, hip osteoporosis is less prevalent in our black populations, although vertebral bone mass, and possibly also vertebral fracture prevalence, in black and white postmenopausal South African women appear to be similar.[22-24]

7.1.3 Previous fragility fracture

A prior fragility fracture after age 40 to 50 years is another important BMD-independent risk factor. The risk is increased fourfold for a vertebral fracture following a previous spine fracture, and this risk increases further with the number of prior vertebral fractures. A vertebral fracture also increases the risk of a future hip fracture. The risk of a subsequent fracture is highest (fivefold) in the first year following the original event.[116-119]

7.1.4 Family history of fracture

A recent meta-analysis of seven large, prospective population studies again reiterates the importance of a parental (particularly maternal) history of fractures (particularly hip fracture) as a largely BMD-independent risk factor for all (but particularly hip) osteoporotic fractures.[120]

7.1.5 Excessive leanness

A low body mass index (BMI) is a well-documented risk factor for fracture that is only partially independent of BMD.[123] The effect of body weight appears to be contributed to by both fat and lean mass, and is probably mediated by a number of mechanisms, including skeletal loading, secretion of hormones from pancreatic beta cells (e.g. insulin, amylin), secretion of bone-active hormones (e.g. estrogen, leptin) from adipocytes, as well as hormones related to nutrition (e.g. IGF-1, GLP-2).[124] A recent meta-analysis of 12 population-based cohorts confirmed that excessive leanness was an important risk factor, particularly for hip fracture, in both men and women.[123] Risk does not appear to be a linear function of mass, and a BMI ranging from 22-18 kg/m^2 has been suggested as cut-off value in various studies. Risk is increased twofold when individuals with a BMI of 20 kg/m^2 and 25 kg/m^2 are compared, yet when the latter are compared to subjects with a BMI of 30 kg/m^2, no halving of risk is observed.[123]

7.1.6 Alcohol

Chronic alcohol consumption decreases bone mass and strength, increases the risk of falling, and has been shown to be the most important lifestyle risk factor for osteoporosis in the Western Cape.[125] Alcohol is directly toxic to bone cells: it decreases osteoblast proliferation and activity, and significantly lowers serum osteocalcin. Bone histology is usually characterised by a reduction in bone formation, but may also show signs of impaired mineralisation if vitamin D insufficiency is present. Chronic alcohol consumption may result in hypogonadism, metabolic acidosis, malnutrition, liver disease and hypovitaminosis D, as well as pseudo-Cushing's syndrome with hypercortisolaemia. Alcohol use is often associated with lifestyle factors, like smoking or lack of exercise, known to adversely influence bone health.[126-128]

Alcohol appears to be a particularly important risk factor in males and in younger females.[129-132] The effect is dose-related and intakes of three or more units daily are associated with a dose-dependent increase in risk. A moderate alcohol intake (fewer than three units per day) in postmenopausal women has, in fact, been associated with *increased* BMD at both the spine and hip. Reasons for this remain unclear, although alcohol is known to increase body mass and estrogen production in adipose tissue, to impair the clearance of exogenously administered estrogen and to stimulate the secretion of the antiresorptive hormone, calcitonin.

7.1.7 Smoking

Smoking is a risk factor that is, in part, dependent on BMD.[133-135] Smoking increases the metabolism of endogenous and exogenous estrogen to inactive derivatives, and is also associated with early menopause and lower body weight. The decrease in fat mass reduces

peripheral conversion of androgens to estrogen, decreases mechanical loading of bone, and diminishes resistance to falls. Smoking also lowers the intestinal absorption of calcium and is often associated with alcohol use and a sedentary lifestyle.

7.1.8 Hypogonadal status

Estrogen deficiency is associated with a decreased BMD, as well as microarchitectural deterioration of bone. A premature menopause/ovarian failure and other causes of hypogonadism are recognised risk factors for osteoporotic fractures.[136-138] Hypogonadism resulting from athletic amenorrhoea, delayed puberty or the prolonged use of the depot progestin contraception, which is so popular in this country, is also a risk factor for osteoporosis in younger individuals. Hypogonadism, often asymptomatic, is an important risk factor for osteoporosis in men, being present in 20-66% of patients presenting with vertebral or hip fractures.[129-132]

7.1.9 Nutritional risk factors

Deficiencies in numerous macro- and micronutrients have been implicated as risk factors for osteoporosis. Their precise role is, however, not easy to ascertain, and evidence-based proof is often lacking. Low calcium intake, hypovitaminosis D and protein-energy malnutrition are accepted risk factors thought to decrease bone strength, increase the propensity to falls, impair fracture healing and prolong rehabilitation.[139-144] Poor calcium intake may occur with ageing or in younger individuals with eating disorders. Intestinal absorption of calcium may be impaired in patients with gastrointestinal disorders (gastrectomy, gastric bypass, pernicious anaemia) and low vitamin D levels, or in the elderly. Hypovitaminosis D occurs with poor intake, low sunlight exposure, increased skin pigmentation, malabsorption, liver disease, obesity or use of drugs that interfere with its metabolism, like the anticonvulsants. Although large protein intakes may increase urinary calcium wasting, most epidemiologic studies in children and pre- and postmenopausal women, as well as in men, have documented a positive correlation between protein intake and bone health. Adequate protein intake is thought to largely mediate its effect through increasing the production and action of IGF-1.[139,143,144]

7.1.10 Falls

More than 90% of hip fractures occur after a fall. The pathogenesis of falls is complex, and various extrinsic (e.g. environment) and intrinsic factors (e.g. impaired balance, poor vision, reduced strength, drugs) are involved (see 10.2).

7.1.11 Glucocorticoid use

Chronic (longer than three months) glucocorticoid use is a major risk factor for fracture that is not solely dependent on bone loss.[150] Glucocorticoids directly inhibit osteoblastic

bone formation.[151] Glucocorticoids directly stimulate osteoclastic bone resorption and, in addition, impair intestinal absorption of calcium and enhance renal calcium wasting. The resultant negative calcium balance causes PTH-mediated bone resorption. Further, glucocorticoids decrease circulating sex hormone levels and may cause muscle weakness, which predisposes to falling (see 10.1.4.1).

7.1.12 Specific diseases

Osteoporosis occurs secondary to a number of diseases, most of which are listed in Table II. Many of these disorders predispose to fracture by predominantly decreasing BMD. Others, for example rheumatoid arthritis, also increase fracture risk independently of BMD.[150]

7.2 Assessment of bone turnover

Various prospective, longitudinal studies strongly support the contention that a high bone turnover is not only associated with increased bone loss,[85,152-154] but that it also increases fracture risk independently of BMD.[155-157] Bone turnover can best be assessed by (i) the measurement of biochemical markers of bone resorption and formation, or (ii) employing quantitative bone histology.

7.2.1 Bone turnover markers

Bone turnover markers (BTMs) are classified as markers of bone formation and markers of bone resorption, even though, in most clinical circumstances when the two arms of the bone remodelling process are coupled, they change in parallel (Table IV).

7.2.1.1 Markers of bone formation

Bone formation is assessed by measuring the enzymatic activity of osteoblasts (e.g. bone-specific alkaline phosphatase, BSALP), bone proteins (osteocalcin) or fragments of procollagens released during bone formation (the C- and N-terminal propeptides of type I collagen, PICN and PINP). Circulating osteocalcin, also called bone Gla-protein (BGP), has a half-life of a few minutes, is rapidly cleared by the kidney, and reveals a circadian rhythm with a peak around 04h00, trough at 17h00, and 15-20% difference between peak and trough levels. Measurement of the intact molecule and/or the large N-terminal-mid peptide (but not smaller fragments) correlates well with invasive indices of bone formation.[158,159] Recently, it has become possible to measure urinary, as well as γ-carboxylated, osteocalcin.[160] Circulating BSALP can be measured by automated immunoassay with a precision error of < 5%, is much more stable than osteocalcin, has a half-life of one to two days and is, therefore, less sensitive to circadian variation and is regarded as the preferred formation BTM by many.[157-159]

7.2.1.2 Markers of bone resorption

Resorption markers can be classified as degradation products released during osteoclastic resorption of bone (C-terminal telopeptides of D-Pyr, CTX; N-terminal telopeptides of D-Pyr, NTX; carboxyterminal telopeptides, ICTP; and pyridinolines), or as osteoclast regulatory protein markers. The latter include markers of osteoclast numbers (TRAcP 5b, cathepsin K) and osteoclastogenesis (RANK, RANKL, OPG) and have been extensively used in drug research, but are still being validated for clinical use.[159] Pyridinoline (PYR) and deoxypyridinoline (D-Pyr) are two non-reducible pyridinium cross-links which are formed extracellularly, between two collagen molecules, and are only released during degradation of mature collagen. PYR has a wider tissue distribution and D-Pyr is more bone specific. Both PYR and D-Pyr are excreted in urine, where they are found as free (±40%) and peptide-bound fragments.

Table IV: Biochemical markers of bone turnover

Bone formation	Bone resorption
Alkaline phosphatase (ALP) • Total ALP • Bone-specific ALP (BSALP)	**Products of resorption** • C-terminal telopeptide (CTX) • N-terminal telopeptide (NTX) • Carboxyterminal telopeptide (ICTP) • Pyridinolines (PYR, D-Pyr)
Osteocalcin or bone Gla-protein (BGP) • Intact molecule • Fragments	**Markers of osteoclast numbers** • TRAcP 5b • Cathepsin K
Propeptides of type 1 collagen • C-terminal propeptide (PICP) • N-terminal propeptide (PINP)	**Markers of osteoclastogenesis** • RANK/RANKL • Osteoprotegerin (OPG)

The telopeptides of collagen comprise the non-helical regions of the type 1 collagen molecule and are measured as the C-telopeptide (CTX), the N-telopeptide (NTX), or a trimeric carboxyterminal telopeptide (ICTP). The telopeptides correlate well with bone histology and calcium kinetic studies and currently provide the main approach to assessment of bone resorption in clinical practice.[161-163] Immunoassays, specifically detecting free PYR, free D-Pyr, CTX, NTX or ICTP in urine or serum, are available. The resorption markers show a circadian rhythm similar to that of formation markers, with a peak in early morning, a nadir in the afternoon and a peak to trough difference of up to 100%, which underscores the importance of the timing of collection. There is no agreement as to the best sample to collect for measurement of resorption markers (24-hour urine collection vs. early morning sample).

7.2.1.3 Clinical uses of bone markers in osteoporosis

During recent years, markers have been used to:

- Identify those at risk of fracture, independent of BMD.
- Identify those at risk of rapid bone loss.
- Help rationalise the choice of osteoporosis therapy.
- Monitor/predict the response to therapy.

To identify those at risk of fracture, independent of BMD. Recent studies support the concept that increased bone resorption can lead to increased bone fragility and fracture by two independent mechanisms. Prolonged increases in bone turnover result in a decreased BMD, which is a major determinant of reduced bone strength. However, increased bone resorption also induces microarchitectural deterioration of bone tissue (e.g. trabecular erosion and perforation) which reduces bone strength, but is not detected by BMD measurement. Combining BMD measurements and bone markers allows for the identification of a subset of individuals that is at much higher risk of hip fracture than those identified by each test alone. Riis et al[155] reported that, within three years of the menopause, women who were classified as "fast losers" had a twofold higher risk of sustaining a vertebral or appendicular fracture during 15-year follow-up than women classified as normal or "slow losers". Moreover, women with both a low BMD and a fast rate of bone loss had a higher risk of subsequently sustaining a fracture (odds ratio, OR = 3.0) than those with only one of the two risk factors. BMD and rate of bone loss predisposed to the same degree, with OR for fracture of 1.9 and 2.0, respectively. In the OFELY study,[153,164] women with DXA-confirmed (dual energy X-ray absorptiometry) osteoporosis plus an elevated serum CTX had an RR of fracture of 55%, which is significantly higher than the risk linked to either an isolated low BMD (39%) or an isolated elevated CTX (25%). Moreover, this study revealed that the 10-year fracture risk in postmenopausal women with osteopenia did not differ significantly from that of controls. The subset of osteopenic women with high levels of BTMs, however, had a fracture risk which approximated that of subjects with DXA-confirmed (T-score < -2.5 SD) osteoporosis.[31] Similar data have been provided by the EPIDOS,[156] Rotterdam[165] and other studies.

In summary: It would seem reasonable to conclude that the combination of a BMD measurement plus BTM profile will enhance the sensitivity of BMD alone. What remains unclear is whether the addition of BTM data to the combination of BMD values *plus* independent CRFs (as outlined in 7.1) adds further value, particularly when weighed against the costs of sampling and biochemical analysis.

To identify those at risk of rapid bone loss. Numerous prospective studies have confirmed the utility of BTMs to identify patient groups at risk of rapid bone loss.[152-154] However, although the correlation between baseline BTM value and subsequent BMD loss

is statistically significant, it is generally not strong enough to use these biomarkers alone to predict BMD changes in an *individual* patient. Serial use (over one to three years) of a combination of markers does improve the predictive ability.

To help rationalise the choice of osteoporosis therapy. Theoretically, high turnover osteoporosis should respond more favourably to treatment with antiresorptive agents (ARAs), whereas a low turnover state may indicate the need for bone formation-stimulating agents. This has been shown to be the case in studies with some (estrogen, calcitonin),[170,171] but not all (bisphosphonates, strontium ranelate),[172-174] anti-osteoporosis agents, and further work is required to validate this hypothesis. Potentially, these markers may also be used to indicate when, and for what period of time, therapy should be given.

To monitor/predict the response to therapy. Employing standard densitometry, a response to antiresorptive therapy only becomes apparent after one or two years. The use of biochemical markers allows for early detection (within three to six months) of those subjects who show an improvement in BMD 24 months later.[166-169] These studies suggest a role for markers in predicting and monitoring the response to antiresorptive therapy much earlier than would be possible using bone mass measurements. However, it is in this context where the inherent limitations of BTMs become clear, particularly when individual patients, as opposed to large patient groups participating in clinical trials, are concerned (see below). BTMs also allow for assessment of adherence to therapy in apparent non-responders (see Chapter 12).

7.2.1.4 Present limitations of markers of bone turnover

Technical variations. Technical difficulties in the measurement of biochemical markers still constitute a major problem in the assessment of *individual* patients. Serum markers have a variability of 5-10%, but some urine markers (e.g. pyridinolines) may have an overall coefficient of variation of up to 35%, despite an analytical precision error of around 10%.[175] Other technical limitations involve *storage stability, variation between assays* and the *lack of internationally agreed standards*.

Biological variations. *Circadian* and *seasonal* variations and variations in the *metabolism and hepatic/renal clearance* of the markers also need consideration in the timing of specimen sampling and in the interpretation of results.

Site specificity. Biochemical markers reflect total skeletal (largely cortical) metabolism and cannot localise a regional (e.g. hip, spine) abnormality in bone metabolism, i.e. markers are *not site specific*.

7.2.2 Bone biopsy

The use of transiliac needle bone biopsies, performed under local anaesthesia and following time-spaced tetracycline labelling, and the development of techniques to prepare non-decalcified histologic sections (in the general histology laboratory, bone is routinely decalcified prior to sectioning, thereby disrupting the distinction between mineralised and non-mineralised bone matrix), allows for the identification and quantification of cellular, mineralised and non-mineralised components of bone. It also allows for the assessment of local bone turnover, and the separate evaluation of bone remodelling and balance. The non-decalcified bone biopsy was primarily developed to distinguish osteoporosis from osteomalacia. Some patients with early osteomalacia exhibit no distinctive radiologic or biochemical abnormalities. Occasionally, unsuspected disease (e.g. myelomatosis, sarcoidosis, hyperparathyroidism) is first diagnosed at biopsy.

A bone biopsy is *not indicated in the vast majority of patients* with *osteoporosis*. It is, however, invaluable in cases where osteomalacia is suspected (gastrointestinal pathology, drugs like anticonvulsants and hepatic or renal osteodystrophy), particularly in the elderly where poor nutrition and vitamin D deficiency not infrequently give rise to a combination of osteoporosis and osteomalacia.

7.3 Ultrasonic bone assessment

The ISCD[176] and other recently published guidelines[3,4] are in agreement that QUS cannot replace central DXA to diagnose osteoporosis or to follow up patients with this disease.

It has been suggested that QUS may be of value as (i) a surrogate method to estimate BMD, (ii) a stand-alone method to assess fracture risk independently of BMD, (iii) a prescreening tool to identify those at highest risk who would then be subjected to further risk assessment using densitometry, (iv) a triage approach in which those at highest and lowest risk are identified (e.g. employing quintiles or tertiles of risk), following which DXA (or biomarkers) could be employed to assess the middle groups and, (v) combined with BMD, to improve fracture risk prediction.

The correlation between DXA-measured BMD and QUS parameters is highly site- and device-dependent, with coefficients of correlation ranging from as high as 0.8–0.9 for certain site-matched studies, to as low as 0.3–0.5 when peripheral QUS is correlated with BMD at the main osteoporotic fracture sites.[176-178] QUS cannot, therefore, be routinely used as a surrogate method to assess BMD. There is, however, mounting evidence to suggest that QUS measures more than mere BMD, and many studies have documented its utility to assess fracture risk (largely hip), independent of BMD.[176-184] The broadband ultrasound attenuation (BUA) variable is thought to be influenced by density and structural parameters, while speed of sound (SOS) appears to be affected by density and elastic properties

of bone. However, the question as to whether the combination of QUS and BMD could improve the prediction of fracture risk has, until recently, remained unclear, since previous studies have yielded conflicting reports. The EPIDOS study[185] supported this contention, whereas the SOF study[184] concluded that, while QUS was a reasonable surrogate for BMD, combining QUS and BMD only modestly improved sensitivity to identify those at high risk of fracture. The debate continued in smaller, cross-sectional studies.

Part of the reason for these disparate results is probably the retrospective nature of many studies, the relatively short follow-up time (less than three years) of most of the prospective studies, and the various ways in which results were reported (relative risk, odds ratios, absolute risk). A recent study on the effect of including heel QUS in a model (employing hip BMD, age, prior fracture, BMI, smoking and alcohol consumption to classify participants into fracture risk groups) to estimate the 10-year absolute risk of fracture in a large cohort of men and women, revealed that approximately one out of five subjects had to be reclassified after inclusion of BUA, with the greatest reclassification (> 30%) occurring in the group with intermediate risk.[186]

It would, therefore, seem reasonable to conclude that it is very likely that the combination of QUS and BMD measurement will enhance the sensitivity of BMD alone to identify those at risk of fracture. A number of fundamental and logistical issues, however, need clarification before QUS can be recommended for this purpose:

- It remains unclear whether the addition of QUS to the combination of BMD values and independent CRFs (as outlined in 6.2.1) adds further value and is cost-effective.
- The standardisation of QUS devices, quality control and uniformity in reporting results clearly needs attention. Ultrasound instruments express the ultrasonic variables (BUA and SOS) as individual empirical values, or as a combined index based on a particular formula (estimated BMD, eBMD; stiffness index, SI; quantitative ultrasound index, QUI). Results are expressed as either a Z-score (age-corrected) or a T-score (compared to that of the young, adult reference mean).
- Intervention cut-points need to be identified, because there is uniform agreement that the T-score-based WHO classification of osteoporosis cannot be extrapolated to determine QUS diagnostic or intervention thresholds.
- Finally, no data exist as to whether patients, who have been identified on the basis of QUS measurements, will benefit from current bone-active drugs.

7.4 NOFSA recommendations on fracture risk assessment

a. ***Clinical risk factors (CRFs) must be included in any assessment.*** As recommended by our previous guideline on the diagnosis and management of osteoporosis,[8] we continue to support a risk factor-based, case-finding strategy, as opposed to population screening, for the management of osteoporosis, and recommend that CRFs should always be included in the assessment of fracture risk (GRADE 1/ØØØØ).

b. ***CRFs differ in importance.*** To be practically useful, Kanis et al have suggested that CRFs should be (i) validated in multiple populations, (ii) adjusted for age, gender and fracture type, (iii) readily assessable by primary care practitioners (e.g. low calcium intake is a recognised CRF for fracture in the elderly, but cannot readily be determined without a food frequency questionnaire), (iv) amenable to therapeutic intervention (e.g. the propensity to falling is an important risk factor, but not amenable to pharmacological intervention), (v) intuitive rather than counterintuitive to medical care (e.g. dementia carries a high risk of hip fracture, but practitioners might not readily recognise dementia as a risk factor for fracture and, therefore, be reluctant to initiate treatment with bone-active medication), and (vi) based on evidence-based medicine.[108,187,188]

c. A low bone mineral density (BMD), prior fragility fracture and advanced age, followed by a low body weight (BMI) and a family history of osteoporosis, are generally regarded as the ***major CRFs*** in otherwise healthy postmenopausal women. Obviously the secondary osteoporoses, including hypogonadism and glucocorticoid-induced osteoporosis (GIOP), become more important in specific settings, while other lifestyle changes (e.g. alcohol) may prevail in certain populations. The propensity to falls becomes increasingly more important with ageing in women, as well as men.[110,111,113-124,189]
In 2003, the WHO embarked on a project to integrate information on CRFs and BMD to improve the prediction of fractures. The result was the release, in 2008, of a WHO Technical Report and an algorithm for assessing the 10-year risk of major osteoporosis-related fracture, including the hip, spine, forearm and humerus.[3,156] The CRFs used in the algorithm had been validated in more than 60,000 men and women from 12 prospective, population-based cohorts, and included age, gender, prior fragility fracture, family history of hip fracture, low BMI, use of oral glucocorticoids, current smoking, excess alcohol intake (three or more units per day), secondary osteoporosis and rheumatoid arthritis. It is recommended that the CRFs identified by the WHO be used to identify subjects at risk (GRADE 1/ØØØO). Use of this algorithm is discussed in Chapter 8.

NOFSA recommendations

NOFSA recommendations

It is suggested that, in addition to those risk factors noted above, evidence of inadequate calcium/vitamin D nutrition and high fall risk be included in the assessment of patients. It is acknowledged that a low calcium/vitamin D intake may be difficult to assess accurately and that a high fall propensity is not necessarily amenable to pharmacological intervention but, given the overall importance of these two additional risk factors, particularly in the elderly, we deem it important to make every effort to identify them (GRADE 2/ØØOO).

d. ***Local research on CRFs is required.*** We agree that many CRFs are universally important and applicable worldwide. We are, however, of the opinion that CRFs differ among populations and recommend that more local research on this topic be undertaken (GRADE 1/ØØØØ).

e. ***Bone turnover markers (BTMs) should not be used routinely, but in selected cases.*** We accept the potential of BTMs in the management of osteoporosis, but are of the opinion that current limitations still impair our ability to assess individual subjects, and therefore do not recommend the *routine* use of BTMs in the care of patients with osteoporosis (USPSTF D/ØØOO). Instead, we recommend that the use of BTMs should be considered in *selected* cases to aid treatment decisions. For example, evidence of a significantly increased bone turnover in an osteopenic (T-score between -1.0 and -2.5 SD) subject may suggest that active intervention with a bone-active drug should be considered, while an absolutely normal turnover may suggest a more conservative, wait-and-see approach (see 7.2.1.3). Whereas we do not recommend the routine use of BTMs to rationalise or monitor therapy, they may be employed to assess adherence to therapy in apparent non-responders (GRADE 1/ØØØO).

f. ***The choice of BTM*** is dependent on availability, costs, technical considerations (accuracy, precision, stability, clearance) and the indication for the measurement.

- Internationally, there is no consensus on the best choice of a BTM, although bone-specific alkaline phosphatase (BSALP) and the telopeptides (CTX and NTX) currently appear to enjoy the widest appeal.
- Serum osteocalcin (intact molecule or the large N-terminal or mid-peptide, but not small fragments) and D-Pyr are acceptable alternatives.
- Serum markers, appropriately collected and processed, generally have a lower variance than urine markers and are, therefore, preferred.
- In osteomalacia, osteocalcin may be less useful, and BSALP is preferred.
- No recommendation can be made as to which BTMs should be used locally, and an urgent need exists to assess the availability, standardisation and

quality control of BTMs in this country. It is, therefore, recommended that NOFSA establish a working group (comprising clinicians and pathologists) to examine this matter (GRADE 1/ØØØO).

g. ***The difficulties associated with the interpretation of BTM data*** are compounded by the lack of any universal definition of what constitutes a "high bone turnover". Assay-specific reference values for various patient populations are generally employed, but are often not sensitive enough to use as intervention cut-points. In the EPIDOS study,[156] bone resorption marker values above the *premenopausal* reference range were associated with a doubling in hip fracture risk in elderly women; hence, this cut-point is often used. We suggest that BTM values *above the premenopausal reference range* be used as an intervention cut-point in pre- and postmenopausal women (GRADE 2/ØØOO).

h. ***Bone biopsy is not indicated in the vast majority of patients*** with osteoporosis, but should be considered in cases where osteomalacia is suspected GRADE 1/ØØØO).

i. ***In the absence of central dual energy X-ray absorptiometry (DXA), quantitative ultrasound (QUS) plus CRFs can be employed to make therapeutic decisions.*** In agreement with the ISCD and other guidelines, we recommend that QUS should not be employed to make a diagnosis of osteoporosis or to follow up patients with this disease (USPSTF D/ØØØO). In the absence of central DXA, QUS of the heel may, however, be used *in conjunction with CRFs* to decide on therapeutic intervention (GRADE 1/ØØOO). A number of studies have demonstrated the value of combining QUS and CRFs,[190-193] none more so than the recently published EPISEM prospective study of 12,958 elderly women, which showed convincingly that the combined use of CRFs and QUS is a valuable tool to assess the 10-year probability of osteoporotic hip fracture.[194] Device-specific thresholds should be employed and results should not be applied to the T-score-based WHO diagnostic classification of osteoporosis (GRADE 1/ØØØO).

j. ***Combining QUS and DXA/BTMs to improve fracture risk assessment cannot be recommended at this stage***. We have taken cognisance of recent reports advocating the value of incorporating QUS into a CRF-BMD programme to stratify fracture risk,[186] but cannot make a recommendation on the *routine* use of combining QUS and DXA at this stage (USPSTF C/ØØOO). Further evidence on intervention cut-points, the cost-efficacy of combining QUS and DXA, and the response to standard drug therapy of subjects identified in this way will be required before an evidence-based decision can be made. Furthermore, data from the original EPIDOS study,[156] as well as the recently published SEMOF study,[195] revealed that, whereas QUS and BTMs

were both useful to discriminate between non-vertebral fracture cases and controls, the combination of these tests was no better than either test alone. Combining QUS and BTMs can, therefore, not be recommended to improve fracture risk assessment (USPSTF D/ØØOO).

8 An integrated approach to fracture risk assessment

The preceding chapters have addressed the diagnosis of osteoporosis and the various additional ways to assess fracture risk. This chapter will attempt to integrate the different risk assessment tools and to provide a holistic approach to selecting patients for osteoporosis therapy. But, first, we need to reiterate the fact that intervention thresholds are not always the same as diagnostic criteria, and remind that the ways in which the results of fracture risk assessment are reported (relative risk, odds ratios, absolute risk, life-time risk, 10-year risk) may be misleading and should be standardised. The new WHO FRAX® risk assessment tool will then be examined, following which an integrated approach to fracture risk assessment is presented.

8.1 Diagnostic criteria vs. intervention thresholds

In the absence of a fragility fracture, the diagnosis of osteoporosis centers on the assessment of bone mass and quality and, since the latter cannot readily be measured, the diagnosis of osteoporosis depends, at present, on the measurement of bone mineral density (BMD). The importance of risk factors other than BMD which predispose to fracture has, however, been emphasised. For this reason, there is a distinction to be made between the diagnosis of osteoporosis and the assessment of risk. This, in turn, implies a distinction between diagnostic criteria and intervention thresholds. Whereas the former have been firmly established,[1,2] the latter remain controversial.

Ultimately, any intervention strategy should aim to provide the care physician with the information to decide whether:

- No further assessment or treatment is required.
- Further assessment is indicated (e.g. further diagnostic tests).
- Treatment is indicated, irrespective of any further diagnostic assessment.

Worldwide, two basic case-finding intervention strategies have been employed. The IOF model,[196] also adopted by the Royal College of Physicians[5] and others, is based on clinical risk factors (CRFs) which dictate the need for BMD testing and, if a T-score of less than -2.5 is found, the patient should be treated. The American NOF model, published in 1998, recommends treatment for postmenopausal women with a T-score below -2.0, or a T-score

below -1.5 in the presence of CRFs.[197,198] The advent of the new WHO risk platform (FRAX®) has created the possibility of a new global case-finding strategy.

Most guidelines agree that patients with T-scores below -2.5 should be treated, and that subjects with T-scores above -1.0 should not. The major controversy involves the group with T-scores between these numbers (i.e. those with osteopenia). In this regard, it should be noted that such decisions are complex and do not only depend on *absolute risk*, but also on the *patient profile* (age, gender, life expectancy, willingness to consider treatment), as well as the *efficacy* and *cost of available treatments*.

8.2 Expression of fracture risk

For many CRFs, epidemiological studies report the risk ratio or relative risk (RR), i.e. the risk of an event in those individuals who have the risk factor(s), compared with those who don't. This may be misleading if the incidence of the underlying event is not apparent. For example, the annual incidence of a deep vein thrombosis (DVT) in healthy postmenopausal women is around 1 per 1,000 individuals. For those on hormone (estrogen) therapy, the incidence is roughly double that, or 2 per 1,000 individuals. Hormone therapy (HT) is, therefore, often stated to "double the risk" of DVT. A more accurate appreciation of the clinical relevance is, however, obtained if the population relative risk (PRR) or *absolute risk* is taken into consideration (i.e. without HT the chances of not getting a DVT is 999/1,000, and on HT it is 998/1,000). The calculation of absolute risk obviously requires knowledge of the incidence of the condition and death in populations.

Another source of confusion is use of lifetime risk as opposed to short-term risk (e.g. 10-year probability). Since the former is dependent not only on the incidence of fracture at different ages, but also on the likelihood of survival (this is why the probability of fracture actually decreases beyond a certain age), data generated may again be misleading. Use of the *10-year absolute risk* has, therefore, become the norm.

8.3 The new WHO risk platform (FRAX®)

8.3.1 The FRAX® tool

This new WHO assessment tool has been widely published,[3.6.199,200] and is also available on the internet (www.shef.ac.uk/FRAX). Briefly, robust CRFs were identified and their relative weights and interactions quantified, along with femoral BMD, in an analysis of 12 prospective study populations (> 60,000 subjects) from Europe (the multicentre EPIDOS and EVOS studies and single-centre studies in Gothenburg, Kuopio, Lyon, Rotterdam and Sheffield), North America (CaMos and Rochester), Australia (DOES) and Japan (Hiroshima).[3,187,188,196] The risk factors included age, gender, femoral neck BMD, BMI, prior fragility fracture

(yes/no), parental history of hip fracture, long-term (more than three months) exposure to systemic glucocorticoids, high alcohol intake (three or more units per day), smoking (yes/no), rheumatoid arthritis, and other putative causes of secondary osteoporosis. The model output is the estimated 10-year probability of either a hip fracture alone or the major osteoporotic fractures combined (hip, spine, wrist and humerus). The FRAX® tool is freely available online to all clinicians and health care professionals.

The FRAX® tool is applied assuming that the interrelations between CRFs and hip BMD with respect to fracture risk are similar among populations. The model is calibrated to the population of interest, based on the incidence of osteoporosis as well as death rates across a range of ages for both men and women in that specific population. To date, some 20 populations have been incorporated in the algorithm, representing those with a *very high risk* of osteoporosis (e.g. Sweden, Belgium, Austria), *high risk* (e.g. USA-Caucasian, UK, Germany, Italy), *moderate risk* (France, Japan, New Zealand), and *low risk* (China, Turkey, African American). It is well established that the risk of fracture may differ as much as 10-fold between countries in Europe alone.[3,6] It is further suggested that, in the absence of a model for a particular country, a surrogate country should be used, based on the likelihood that it is representative of the index country. Clearly, data on hip fracture incidence and death rates are required in order to make this choice. Moreover, the model does not signify an intervention threshold, it merely indicates a fracture probability. In order to determine an intervention threshold, a cost-effective analysis to estimate the levels of fracture risk above which it is reasonable to consider treatment must be performed. For example, such analyses were performed for the USA, incorporating country-specific estimates of fracture incidence, morbidity, mortality and intervention costs, following which it was concluded that treatment was deemed cost-effective when the 10-year hip fracture probability is ≥ 3%, or when the 10-year major osteoporosis-related fracture probability is ≥ 20%.[201,202]

8.3.2 Clinical utilisation of the FRAX® tool

One of the strengths of the WHO tool is its versatility and utility in clinical practice.

Potential scenarios include:

- The tool, *based on CRFs alone,* is used to assess the 10-year absolute risk of fracture. Subjects are categorised into those with a high, intermediate or low risk. Patients at high risk are treated without any further intervention. Those at intermediate risk are reassessed with a BMD measurement, following which a decision is made to treat or not.
- The tool, *based on CRFs with or without BMD data*, is used to assess risk, following which a treatment decision is made.
- Use of the tool, *based on CRFs with or without BMD*, is limited to subjects with osteopenia (T-score between -1.0 and -2.5).

The first scenario is largely suggested for countries with very limited access to central DXA.[3,203] The second is the predominant model proposed by the WHO/IOF,[6] whereas the last scenario has been adopted by the American NOF.[4]

8.3.3 Strengths and limitations of the FRAX® tool

The major strength of the new assessment tool is the identification of robust CRFs, thought to be globally applicable to most populations, and assessment of their relative importance and interactions, along with BMD, to predict the probability of an important osteoporotic fracture within a defined period of time (i.e. to determine 10-year absolute risk), and thereby allowing for the identification of subjects at highest risk of fracture. This methodology brings the field of osteology into line with cardiovascular disease and breast cancer risk assessment models, and should prove to be most valuable, not necessarily in cases with proven osteoporosis where the need for treatment is apparent, but particularly in the large intermediate group of individuals with osteopenia.

A major strength of the model is its utilisation of not only the relative importance of different CRFs, but also the fact that *CRFs are interactive and cumulative* in their predisposition to fracture. This is illustrated in both the dichotomous (yes/no), and the continuous (e.g. age and BMI risk variables). For example, while glucocorticoids (2 x), smoking (2 x) or alcohol (2 x) approximately double the fracture risk in a 65-year-old woman, any combination of two of these variables increases the risk threefold (3 x). The combination of all three risk factors increases the risk fivefold (5 x). Furthermore, despite quantitative differences in the 10-year absolute risk for hip fracture between various populations, the average fracture rate for a 75-year-old woman with a BMI of 20 is double that (4 x) of a 75-year-old woman with a BMI of 25 (2 x) which, in turn, is double that of a 70-year-old with a BMI of 25 (1 x), but similar to a 70-year-old with a BMI of 20 (2 x).

While FRAX® is a well-validated tool, it obviously has a number of limitations which can be summarised as follows:

- Epidemiological data on the incidence of hip fracture and mortality rates in specific populations are required before the model can be applied. In the absence of a model for a particular country, provision is made to select a surrogate country, based on the likelihood that it is representative of the index country. Some knowledge about local fracture rates will, however, still be required to select an appropriate surrogate.
- The FRAX® model provides an estimate of the 10-year absolute fracture risk, and was never intended to suggest an intervention threshold. In order to determine an intervention threshold, a cost-effective analysis to estimate the levels of fracture risk above which it is reasonable to consider treatment must be performed for a particular population.

- A number of important CRFs, including low vitamin D and the propensity to falls, as well as biomarker data, are not included in the model.[204]
- More than one recent publication has shown that assessment of vertebral fracture (not specifically included in FRAX®), age and BMD have the highest gradient of risk (GR), and predict the risk of vertebral fractures as well, if not better than, FRAX®.[205,206]
- The model does not take into account dose responses for several CRFs. For example, the nature and number of prior fractures are not specified at all, whereas it is well established that a *prior vertebral fracture* carries an approximate twofold higher risk than other prior fractures. Two prior fractures also carry a much higher risk than a single previous fracture. The total exposure and dose of glucocorticoids or tobacco use, and the nature of the secondary osteoporosis, are further examples. Other than glucocorticoids and rheumatoid arthritis, the secondary osteoporoses are assumed to impact on fracture risk entirely through their effects on BMD. It is for this reason that checking the "secondary causes" box in FRAX® does not alter the risk scores once BMD has been entered. This may hold true for some of the secondary causes, but is certainly not the case for all.
- The FRAX® algorithm uses T-scores for femoral BMD. Although total hip BMD can be used interchangeably, the model cannot accommodate spine T- or Z-scores.
- FRAX® uses femoral T-scores based on the NHANES III *young Caucasian female* reference values (see 6.1.2.1). If DXA measurements are done using gender- and race-specific reference values, T-scores for all men and non-Caucasian women must first be converted to the young Caucasian female reference standard before they can be used in FRAX®.
- The WHO algorithm cannot assess young individuals below age 40 years.
- The efficacy of bone-active drugs to reduce fracture rate has largely been documented in subjects selected on the basis of a low BMD and/or prior fracture. Little data are available as to the efficacy of these drugs in patients selected otherwise.
- Recent analyses suggest that, when the 3% hip fracture probability intervention threshold is applied to American postmenopausal female populations, approximately 40% of all Caucasians over the age of 50 years, 72% over 65 years, and no less than 93% over 75 years will require pharmacological treatment.[207,208]

8.4 NOFSA recommendations on an integrated approach to managing osteoporosis in postmenopausal women, and men over the age of 50 years

a. ***We recommend that treatment should be considered when a prior fragility fracture is present,*** regardless of the results of a bone mineral density (BMD) measurement. This approach is supported by both the American NOF[4] and the WHO/European Guidance[3] (GRADE 1/ØØØO). The WHO strategy does not specify the nature of the fragility fracture, whereas the new NOF guide specifically refers to prior hip or vertebral fractures.[4] It is suggested that treatment be initiated on the basis of a typical osteoporotic fracture, i.e vertebra, wrist, hip, pelvis, rib or humerus. Vertebral and multiple fractures should, however, carry more weight in making a decision to treat or not (GRADE 2/ØØOO).

   This does not imply that a BMD measurement should not be performed whenever possible, since it adds significantly to the overall management of patients with osteoporosis (see 6.2).

b. ***We recommend that treatment should be considered when the dual energy X-ray absorptiometry (DXA) T-score is ≤ -2.5 at the hip or spine.*** The specificity of DXA and its utility to predict fractures have been alluded to previously (see 4.2 and 6.1.2.) (GRADE 1/ØØØO).

c. ***We recommend that treatment should be considered in patients with osteopenia (T-score -1.0 to -2.5), under certain circumstances.*** Given the lack of sensitivity of BMD measurements to adequately identify those at risk of fracture, the various options to improve sensitivity by combining BMD measures with clinical risk factors (CRFs) and other assessment tools were discussed (see 7.1). Three approaches may be considered to manage individuals with osteopenia:

   - ***Consider the FRAX® tool.*** This option is confounded by the fact that, at present, no fracture data exist for the different populations in South Africa, so that even the choice of a surrogate country is problematic. Moreover, no health economic strategy has been formulated for the treatment of osteoporosis, so that it is not possible to recommend at which absolute 10-year risk level intervention would be appropriate. We have also taken cognisance of other limitations of this algorithm. Nonetheless, if a subject is clearly of, for example, British, German or Dutch descent, it is probably reasonable to employ the model using this index country and a 3-5% hip intervention cut-point. It should, however, be emphasised that this option will provide only a crude estimate of risk, as well as indication to intervene (GRADE 2/ØOOO).

- ***Consider other risk assessment tools.*** The FRAX® model is not the only 10-year fracture risk assessment tool available. The most recently introduced fracture risk algorithm, the QFractureScore, was developed with data collected from 357 general practices (1,183,663 female patients and 1,174,232 male patients) in the UK.[209] Many risk factors not included in FRAX® are included (e.g.fall propensity) and the model can be used in young subjects and does not require BMD measurements. The robustness of CRFs used and the applicability of this model to different populations are, however, unclear and it cannot be recommended at present (USPSTF D/ØOOO).
- ***Individual assessment of CRFs and BMD.*** Figure 4 depicts a simple algorithm, incorporating FRAX®, which is suggested for the management of individuals over age 50 years with osteopenia (GRADE 2/ØØOO). Note that the use of FRAX® is limited to subjects with osteopenia, similar to that proposed by the new American NOF Guide,[4] and not as a tool to determine initial intervention thresholds in all subjects, as proposed by the WHO.[3]

d. It is further suggested that the ***major CRFs*** (other than a prior fracture or a BMD in the osteoporosis range, which would indicate the need for treatment in any event) ***be used to decide on intervention,*** namely age, low BMI, family history of osteoporotic hip fracture, lifestyle (alcohol, smoking), fall propensity and the secondary osteoporoses, including those caused by glucocorticoids and hypogonadism. Age over 75 years is generally agreed upon as an intervention threshold, and is sufficient to generate a 10-year hip fracture probability of > 3% in nearly all white women and men according to FRAX®.[3,4] Likewise, the presence of two or more of the noted CRFs in osteopenic subjects aged ≥ 65 years can be regarded as an indication to intervene.[3-7] The situation in subjects ≤ 65 years of age is, however, more complex and requires individualisation, and should be guided by the nature and particularly the number of CRFs, coupled with the severity of the osteopenia. These are also the individuals who should, preferably, be managed by care physicians with expertise and experience in osteology (GRADE 2/ØØOO). We recommend that intervention in children only be initiated when a low BMD is coupled with a clinically significant fracture history (see 6.1.2.1).

e. ***If the need to intervene is still not apparent,*** despite careful consideration of CRFs and BMD data, a decision can be made to either (i) employ BTMs (intervene if BTM values exceed the upper limit of the premenopausal reference range) or (ii) adopt a conservative wait-and-see approach and reassess in 18-24 months (GRADE 2/ØØOO). We do not recommend the addition of other risk assessment tools, in particular QUS or QCT, at this stage (USPSTF D/ØØOO).

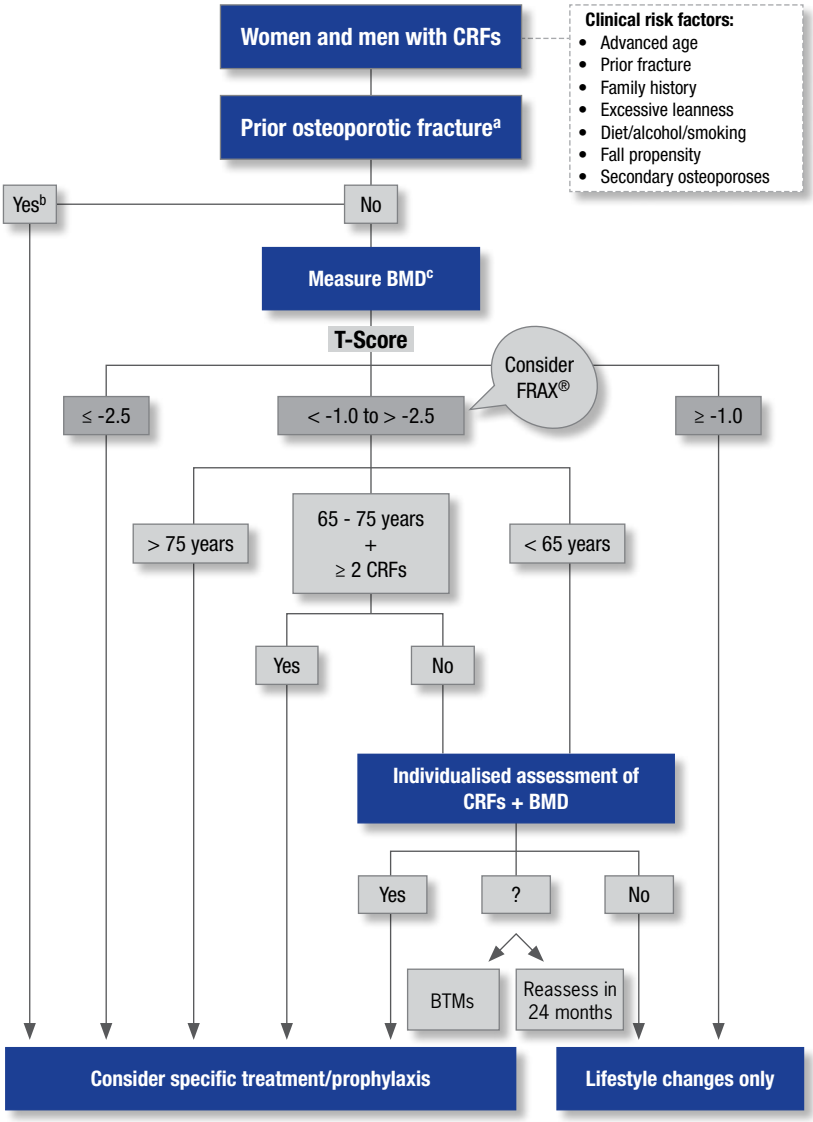


Figure 4: Algorithm for the management of osteoporosis in postmenopausal women and men aged 50 years and older

[a] Fracture of wrist, spine, hip, rib, pelvis or humerus.
[b] Also measure BMD.
[c] Hip, spine ± wrist.

f. ***Treatment decisions should always be individualised*** (GRADE 1/ØØØØ). Algorithmic recommendations should never replace good clinical judgement. This is particularly true for men and younger patients for whom few, if any, guidelines exist. Moreover, given the current extent of our knowledge, it is certainly not ethically justifiable to refuse treatment to, for example, men or non-Caucasian women with a particular clinical profile simply because their risk quantification is not as high as that of Caucasian women with the same clinical profile.

g. ***We strongly recommend the need to assess the incidence of osteoporotic fractures in different South African populations,*** following which a health economic strategy should be formulated for the treatment of osteoporosis in this country (GRADE 1/ØØØØ).

9 Clinical and laboratory assessment

A detailed general and dietary history, full physical examination and appropriate laboratory assessment are required in all patients prior to the initiation of treatment for osteoporosis. The aims of these assessments are to (Figure 5):

- Confirm the diagnosis of osteoporosis and rule out other metabolic bone diseases (primary hyperparathyroidism, osteomalacia) as the cause of low bone mineral density (BMD).
- Identify an underlying disease as possible cause of the osteoporosis (endocrinopathies, malignancies, systemic diseases, bone-toxic drugs) (Table II).
- Identify lifestyle factors which may affect bone health adversely (diet, alcohol, smoking, sedentary lifestyle), and risk factors for falls (Table VIII).
- Characterise the severity and nature of the osteoporosis:
  - Assess the severity (BMD, radiological evidence of fracture);
  - Determine sites involved (spine, hip);
  - Measure bone turnover in selected cases (biomarkers).
- Assess patient preferences, compliance, potential drug side-effects, and financial resources.
- Rationalise and initiate therapy.
- Use baseline data to monitor the response to therapy and to reassess therapeutic options.

9.1 Tests to exclude metabolic bone diseases other than osteoporosis

A limited assessment of calcium homeostasis usually suffices to exclude causes of a low BMD other than osteoporosis.

Serum calcium and phosphate levels are normal in uncomplicated osteoporosis, but altered in patients with *primary hyperparathyroidism* or *osteomalacia*. To exclude these relatively rare, but readily treatable, causes of a low BMD, confirmation of normal serum calcium and phosphate is essential in all patients presenting with apparent osteoporosis. The total serum calcium should always be corrected for the serum albumin level. Alternatively, a free (ionised) calcium value may be obtained, provided a reliable assay is used.

Sensitive assays for serum PTH and 25-hydroxyvitamin D (25OHD) are now available to exclude primary and secondary hyperparathyroidism. Measurable serum PTH in the

presence of hypercalcaemia is diagnostic of primary hyperparathyroidism. Secondary hyperparathyroidism is suggested by an increased serum PTH level in the face of a low serum 25OHD and/or low urinary calcium. Osteomalacia usually results from a vitamin D or phosphate deficiency/abnormality, and is suggested when the serum calcium or phosphate levels are decreased and alkaline phosphatase (ALP) is elevated. Rarely, serum biochemistry is only marginally disturbed and bone histology is required to confirm a diagnosis of osteomalacia (see 7.2.2).

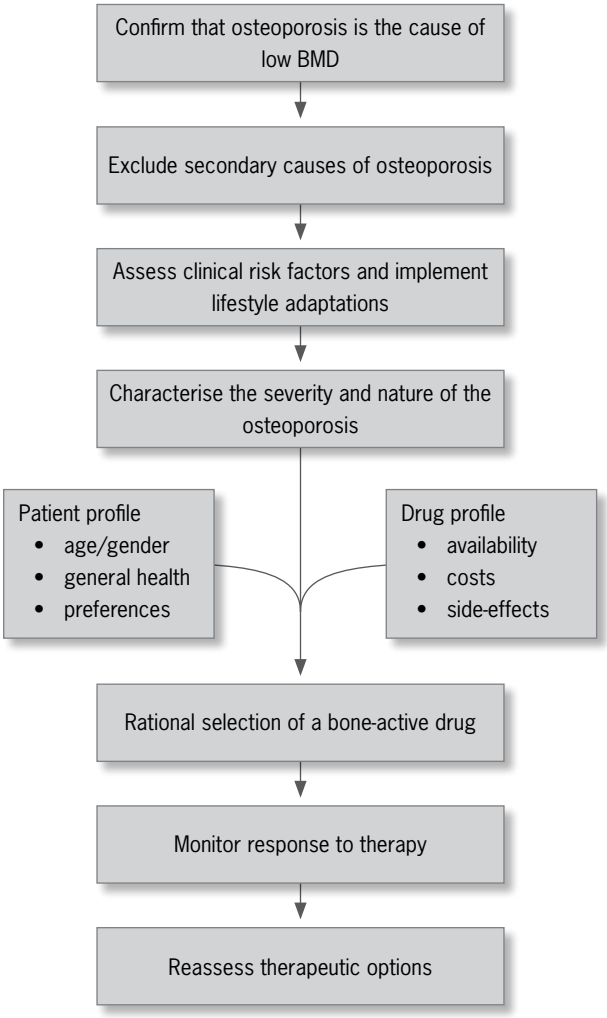


Figure 5: Algorithm for the assessment of patients with osteoporosis

Serum 25OHD is low in many elderly patients, particularly when institutionalised (see 7.1.9). There is general agreement that serum 25OHD levels < 10 ng/ml (25 nmol/l) indicate frank vitamin D deficiency, while levels > 30 ng/ml (75 nmol/l) suggest a vitamin D-replete state. Some controversy still exists as to whether a value < 20 ng/ml or < 30 ng/ml should be regarded as vitamin D insufficiency. Michael Holick defines *vitamin D deficiency* as a 25OHD level below 20 ng/ml, *vitamin D sufficiency* as a value at or above 30 ng/ml, and *vitamin D relative insufficiency* as a value between 21 and 29 ng/ml.[210,211]

Since it is often unclear whether mean or minimum levels are being referred to, and given seasonal, assay (e.g. the Roche Elecsys® assay exclusively measures $25OHD_3$, whereas other assays measure both $25OHD_2$ and $25OHD_3$) and other variables, this controversy is likely to remain unresolved for some time.[212-215] Recent surveys in the UK and Europe[214,216-218] have suggested that as little as 16-18% of the general population aged over 65 years have 25OHD levels > 30 ng/ml. This value may fall to as low as 4% in hip fracture cases. Moreover, frank vitamin D deficiency (< 10 ng/ml) was present in 8-15% of the general population, and in up to 50% of those with hip fracture. Radiologically detected Looser zones and/or histological evidence of osteomalacia have been shown to be present in up to 37% of hip fracture patients.[219] Secondary hyperparathyroidism resulting from vitamin D insufficiency is known to be present in > 50% of hospitalised patients, with or without hip fractures.[220,221] A sunny climate does not exclude osteomalacia, and Looser zones have been documented in 10% of hip fracture patients in Qatar.[222] Locally, the vitamin D status of patients with osteoporosis has not been formally studied, although the in vitro formation of vitamin D has been shown to be particularly poor in Cape Town during winter, suggesting that hypovitaminosis D should not be disregarded in our populations.[223]

Urinary excretion of calcium is normal in most patients with osteoporosis. Low 24-hour urine calcium suggests poor calcium intake or absorption. Hypercalciuria indicates increased intestinal absorption of calcium, a primary renal calcium leak and/or accelerated bone resorption. The latter occurs, not infrequently, during periods of immobilisation, particularly when bone turnover is increased (e.g. hyperparathyroidism, hyperthyroidism, following a fracture, during the early menopause, or in the young). Approximately 10–20 % of young men who present with idiopathic osteoporosis have hypercalciuria, with or without renal stones.[224,225] Given the fact that calcium (± vitamin D) supplementation is widely utilised in the management of osteoporosis, a urine calcium level should be obtained prior to such intervention.

9.2 Tests to identify underlying causes of osteoporosis

It is conventional to classify the osteoporoses into primary (idiopathic) and secondary types, based on the apparent presence or absence of predisposing causes. This is not only artificial (every type of osteoporosis must have some cause), but may also be misleading. It is often stated that secondary causes of osteoporosis are found in up to 30% of women, and in more than 50% of men, presenting with symptomatic vertebral fractures.[225] In men, hypogonadism,

exogenous bone toxins (alcohol, glucocorticoids) and idiopathic hypercalciuria are common risk factors. The pathogenesis of osteoporosis is, however, multifactorial and, in order to optimise patient management, all probable risk factors should be identified.

9.3 NOFSA recommendations on the assessment of patients with osteoporosis

a. ***Serum calcium, phosphate, albumin, PTH and ALP*** levels should be determined in every patient with apparent osteoporosis to exclude primary hyperparathyroidism and osteomalacia (GRADE 1/ØØØO). ***Serum 25OHD*** should be obtained in all elderly patients and, in particular, those who are institutionalised, are house-bound or have low sunlight exposure (including the use of sun blockers and for religious reasons), have increased skin pigmentation, are obese, have suspected malnutrition, malabsorption or liver disease, or use drugs that interfere with vitamin D metabolism, like the anticonvulsants.

b. ***Biochemical tests to identify causes of osteoporosis should largely be dictated by clinical assessment,*** and few tests should be performed routinely (GRADE 1/ØØØO). A limited number of tests are, however, justifiable in order to identify underlying causes of osteoporosis, particularly if the diseases thus identified may require treatment in their own right. No consensus exists as to which laboratory test should be included,[225,226] and none of the current guidelines make recommendations in this regard.

c. ***A full blood count and ESR, serum protein electrophoresis, sex hormone levels in males, and females when the menopausal state is uncertain, and a urine calcium level*** may provide important information and should be routinely included in the evaluation of patients with established disease (GRADE 2/ØOOO).

d. ***A number of optional tests,*** which should be considered under specific clinical circumstances, are also suggested (GRADE 2 / ØOOO). These are listed in Table V.

Table V: Recommended laboratory and radiological procedures for osteoporosis

Routine assessment

- History, physical examination and urinalysis: clinical risk factors and falls assessment.
- Bone mass measurement: spine and hip (distal radius if spine and hip data invalid).
- Vertebral fracture assessment: standard X-rays or dual energy X-ray absorptiometry-based vertebral fracture assessment (DXA-VFA).
- Serum calcium, albumin, phosphate, PTH and ALP.
- Full blood count and ESR.
- Serum TSH.
- Serum protein electrophoresis.
- Serum FSH, and estradiol in premenopausal women or women in whom menopausal state is unknown.
- Serum total testosterone in men.[a]
- Serum creatinine.
- Urine calcium and creatinine (preferably a 24-hour collection).
- 25OHD (all elderly, institutionalised, non-sunexposed, malnourished).

Optional assessment

- Serum or urine bone turnover markers (selected cases, as detailed in 6.2.4).
- Liver transaminases (alcohol abuse/liver disease is suspected).
- Serum T_4 and T_3 (thyroid disease is suspected/TSH level is abnormal).
- Bone biopsy with quantitative histomorphometry (osteomalacia suspected).
- Bone marrow aspiration, isotope bone scan, cancer markers.

[a] Most commercial assays of total serum testosterone employ a lower limit of normal of 9-12 nmol/l. It is suggested that levels above 12 nmol/l be regarded as normal, and levels below 8 nmol/l as decreased. Levels between 8-12 nmol/l, particularly when accompanied by symptoms of hypogonadism, should be examined further (e.g. serum free testosterone, LH, FSH).

10 Non-pharmacological management of osteoporosis

Non-pharmacological measures to prevent osteoporotic fractures are essentially aimed at (i) the improvement of bone strength and (ii) the prevention of falls.

10.1 Non-pharmacological measures to improve bone strength

These largely involve nutritional measures, physical exercise, limiting alcohol consumption, stopping smoking, and avoiding bone-toxic drugs.

10.1.1 Healthy eating plan

Many nutritional factors have been implicated as possible causes of osteoporosis. A healthy eating plan, containing the correct amount of energy and all essential nutrients (including calcium and vitamin D), with sufficient but not excessive protein, appears to be the most important dietary measure to help prevent this disease.

10.1.1.1 Calcium and vitamin D

We have taken note of the more common causes of calcium and vitamin D deficiency (see 7.1.9), as well as the assessment of calcium and vitamin D (measured as 25OHD) status (see 9.1). We shall now briefly review the effects of calcium/vitamin D on (i) peak bone mass attainment, (ii) age-related bone loss, (iii) pregnacy and lactation and (iv) fracture risk.

Peak bone mass attainment. Retrospective epidemiological studies of calcium nutrition in populations aiming to explain differences in the prevalence of osteoporosis and fracture, have generally produced conflicting results, which is not surprising, given the fact that calcium intake is difficult to assess. Nonetheless, observational studies have suggested that the largely genetically determined peak bone mass is augmented by a high calcium intake.[227] This has also been shown in an Australian co-twin study.[228] Randomised, double-blind, placebo-controlled intervention trials have concluded that calcium supplementation increases the gain in bone mass, although the magnitude of the effect appears to vary depending on dose, baseline calcium intake, skeletal sites examined, pubertal maturation and genetic factors, including vitamin D receptor polymorphism.[229-231] A recent meta-analysis, which reviewed 19 calcium intervention studies in children, concluded that calcium

supplementation resulted in a small, but significant, increase in total body bone mineral content.[140]

Age-related bone loss. Calcium deficiency has a more pronounced effect on age-related bone loss, and intervention later in life appears to be more beneficial. Heany reviewed the data from 19 calcium intervention studies and concluded that calcium slowed or stopped bone loss in 16 of the 19 studies.[232] Dawson-Hughes et al originally showed that supplemented calcium significantly reduced both trabecular and cortical bone loss in older women but, in women less than 5 years postmenopausal, it had no effect on trabecular bone loss.[233] The beneficial effect of calcium supplementation was largely confined to subjects with a low dietary calcium intake (< 400 mg per day). Employing larger doses of supplemented calcium, Reid et al later showed that bone loss could be arrested, irrespective of dietary intake.[234] A number of studies, including a recent review of 31 trials, have suggested that calcium, when combined with either exercise or estrogens, has additive effects.[235,236]

Severe prolonged vitamin D deficiency induces osteomalacia, but less marked deficiency causes secondary hyperparathyroidism, an increase in bone turnover and osteoporosis. Vitamin D is obtained from two sources: dietary intake and cutaneous production. The ability of the intestine to absorb vitamin D decreases with as much as 40% with age. Exposure to sunlight, as well as the synthetic capacity of the skin, also decreases with age. Until 1997, the recommended intake of vitamin D was 200 IU daily. In 1998, the American NOF recommended 400 IU per day for those below 70 years of age, and 800 IU per day for those older than 70.[197] Currently, the NOF recommends 800–1,000 IU per day.[4] For every 100 IU vitamin D ingested, the serum 25OHD increases by approximately 1 ng/ml.[237,238] When administered in doses of 400–800 IU per day, vitamin D by itself probably has little effect on BMD, except among subjects who have frank vitamin D deficiency.[239] Vitamin D, when administered in doses of 700-1,000 IU per day, has also been shown to improve muscle strength and to reduce falls.[240,241] Other non-skeletal effects of vitamin D include alterations of adaptive and innate immunity; cardiovascular effects; possible cancer (colon, breast) prevention; modulation of diseases like diabetes mellitus, multiple sclerosis, depression and schizophrenia; and a significant decrease in cardiovascular and all-cause mortality.

Pregnancy and lactation. The doubling of the intestinal absorption of calcium early in pregnancy, an effect that is only explained in part by the increase in maternal 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), appears to largely meet the additional demand for calcium imposed by the growing foetus. Biomarkers of bone resorption and bone histomorphometry increase only modestly, and the maternal bone mineral density (BMD) remains unchanged, or decreases by less than 5%, one to six weeks after delivery. Trabecular bone loss occurs rapidly during lactation, but recovers during weaning. There is little evidence that calcium supplementation during pregnancy or lactation significantly

influences the severity of bone loss or the rate of recovery following weaning, and further studies are required.[242-244]

Vitamin D deficiency is common in women of childbearing age and during pregnancy, and may result in neonatal hypocalcaemia, rickets and possibly low bone mass in later childhood, poor intrauterine growth and an increased risk of diseases, like diabetes and asthma. Supplementation with ≤ 400 IU vitamin D is inadequate to raise maternal 25OHD, and doses of 2,000-4,000 IU/day are probably necessary to prevent vitamin D deficiency.[244]

Fracture risk. Earlier studies showed that calcium and vitamin D supplementation significantly reduced the risk of non-vertebral or hip fracture.[245-247] Meta-analyses in 1997[248] and in 2005[249] suggested that supplementation with 1 g of calcium, plus vitamin D 800 IU per day, was associated with a 20–25% reduction in hip fracture.

A number of recent publications have, however, challenged the anti-fracture efficacy of calcium and vitamin D.[250-256] Many of these studies did not target individuals at high fracture risk, often a low dose of vitamin D (≤ 400 IU per day) was administered and, frequently, compliance was poor. For example, the large WHI study of more than 36,000 postmenopausal women reported a significant increase in hip bone density, but no reduction in hip fracture, following daily supplementation with 400 IU vitamin D and 1,000 mg elemental calcium. Yet, when the non-adherent (defined as taking less than 80% of the assigned study drug) individuals (40%) were excluded, and only those subjects who were compliant were analysed, a highly significant 29% reduction in hip fracture, compared with the placebo group, was documented.[256] Likewise, whereas 1,200mg calcium per day for five years was reported as ineffective in reducing fracture risk in a group of elderly women, the 57% of subjects who took at least 80% of the medication showed a 34% reduction in fracture risk.[254] In a meta-analysis of nine RCTs, including more than 50,000 patients, Boonen et al concluded that vitamin D alone did not significantly reduce the risk of hip fracture; the addition of calcium, however, resulted in a 28% reduction in hip fracture risk.[141] A recent Cochrane review, which included 45 trials with 85,000 participants, also concluded that vitamin D alone is unlikely to be effective in preventing hip or vertebral fractures, but that the combination of calcium plus vitamin D resulted in an approximate 15% reduction in hip fracture.[257]

Clearly, the effect of calcium and vitamin D on fracture prevention is complex and influenced by many factors. Key role players appear to be the dose of vitamin D (doses of 700–1,000 IU/day are generally effective, whereas a dose of ≤ 400 IU/day is not), and adherence to therapy. Calcium supplementation is associated with gastrointestinal side-effects (see below) and adherence is often below 50%. Other factors which have been implicated include baseline calcium/vitamin D nutrition, age and general health, body mass (obesity results in the sequestration of vitamin D and the requirement for higher doses to achieve vitamin D repletion),[258] skeletal sites assessed (cortical vs. trabecular bone), whether the supposedly

more potent cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2) was used, and whether primary or secondary (i.e. prior fracture present) prevention was attempted. In the most recent meta-analysis of 12 RCTs for non-vertebral fractures (n = 42,000) and eight RCTs for hip fractures (n = 41,000), Bischoff-Ferrari incorporated adherence to treatment as well as dose of vitamin D (and higher serum 25OHD achieved), and concluded that vitamin D in doses of 500-800 IU/day reduced hip and non-vertebral fractures by approximately 20%, an effect that was independent of calcium supplementation.[259]

Recommended calcium intake. There is remarkable uniformity in the recommended daily intake of calcium to ensure optimal bone health suggested by the American NOF (www.nof.org/prevention/calcium2.htm), the NIH (http://dietary-supplements.info.nih.gov), the IOF (www.iofbonehealth.org) and other bodies, including our own NOFSA (http://www.osteoporosis.org.za) (Table VI). Dairy products are the most readily available source of calcium, while some green vegetables (e.g. broccoli), sardines and nuts are also rich in calcium. Some foodstuffs, including dairy products, are calcium fortified. If the recommended daily allowance (RDA) cannot be achieved by dietary intake alone, pharmacological supplementation is necessary. It should be emphasised that these recommendations are only applicable to Caucasians leading a Western lifestyle, since some evidence exists that African Americans and black South Africans are more efficient at conserving calcium and probably do not need so much calcium in their diets.

Table VI: Optimal calcium requirements

Group	*Daily intake (mg)*
Infants	
Birth – 1 year	500
Children	
1 - 5 years	500
6 - 10 years	800
Adolescents/young adults	1,200
Adult women and men	
25 - 65 years	1,000
Pregnant and lactating	1,200
Over 65 years	1,200

Safety and side-effects. Gastrointestinal side-effects, most notably constipation, occur with calcium supplementation, while vitamin D is associated with a 17% increase in the risk of kidney stones.[256,257] Whereas an adequate dietary calcium intake is generally associated

with a reduction in cardiovascular risk, Bolland et al recently reported an increased incidence of cardiovascular disease in subjects taking relatively high-dose calcium supplements.[260] This is fully discussed in 11.1.1.

10.1.1.2 Other dietary measures

Protein-energy malnutrition decreases bone formation and is associated with hypogonadism, muscle weakness and an increased risk of falling. Many elderly fracture patients are malnourished and dietary supplementation of hip fracture patients with 20 g protein for 30 days has been shown to result in the attenuation of proximal femur bone loss, lower mortality and shorter hospital stay.[261] *Eating disorders* like anorexia nervosa are associated with low bone mass, which results from hypogonadism, malnutrition, hypovitaminosis D and other hormonal disturbances, including hypercortisolaemia. *A high protein and phosphate intake* may cause hypercalciuria and secondary hyperparathyroidism, as well as qualitative microarchitectural abnormalities in bone. *High intakes of fibre, phytate and oxalate* impair intestinal absorption of calcium, whereas a *high sodium intake* enhances urinary calcium excretion. *Caffeine* has been shown to promote urine calcium wasting, although this has not been confirmed conclusively. *Vitamins C, B_6 and K* are essential for the synthesis of bone proteins, while a number of *trace elements,* including zinc, copper, boron and manganese, are thought to reduce bone loss, particularly in the elderly. Long-term prospective studies to substantiate the proposed role of these nutrients in bone health are, however, required.

10.1.2 Physical exercise

Adequate exercise is important for normal bone formation, while immobilisation results in rapid bone loss, which is thought to be largely mediated by unopposed bone resorption. Sedentary women are more likely to develop progressive bone loss than active women, and athletes (e.g. tennis players) have a higher BMD in their dominant limb. Large geographic differences in fracture prevalence are thought to relate, at least in part, to differences in physical activity between communities. Physical exercise is an important determinant of the rate of bone loss in later life, but exercise has also been shown to augment peak bone mass. The beneficial effect of exercise on peak bone mass appears to be more pronounced if exercise is started early, and an additive effect between physical activity and pubertal development has been suggested.

The positive effects of a two-year back-strengthening programme in reducing vertebral fractures have been shown in an RCT with a 10-year follow-up. At 10 years, BMD was significantly higher and the RR of compression fractures 2.7-fold lower in the exercise group.[262] More recently, squat and dead-lift exercises for 10 minutes per day, two days per week, were shown to be more effective than estrogen therapy in preventing postmenopausal bone loss.[263]

In 1997, a meta-analysis of 18 studies suggested the beneficial effect of exercise in preserving BMD at the spine, but failed to show any effect on hip bone mass.[264] A subsequent meta-analysis of 25 RCTs revealed a beneficial effect at both the spine and hip in pre- and postmenopausal women.[265] A Cochrane review of 18 RCTs in 2009 showed that, whereas aerobic exercises improved the BMD of the spine, walking increased the BMD of both the spine and hip in postmenopausal women.[266] One reason for these apparent discrepant observations is the fact that few studies assessed the influence of the speed of walking on study end-points. Borer et al, however, recently documented that walking 5 km per day, for four days per week, at a brisk pace above 6 km/hour and achieving a heart rate greater than 82% of the age-specific maximum, increased leg and total body BMD after 15 weeks in postmenopausal women, whereas training at lower intensity increased aerobic fitness, but had no effect on BMD.[267]

Exercise has also been shown to alter skeletal geometry (radiology, ultrasound) and bone turnover (biochemical markers), which is not necessarily reflected in bone mass measurements. Moreover, studies have shown that exercise intervention can improve muscle strength and neuromuscular performance in the elderly. Specific resistance exercises for the back, as well as the walking programme for hip protection alluded to earlier, require a fair amount of skill, strength and fitness. In the elderly, particularly those with painful fractures or other dysfunction, these exercise goals may not be readily achievable. Here, the expertise of a professional physiotherapist is particularly valuable.

Exercise may also adversely influence the skeleton. Excessive exercise (e.g. marathon runners, ballet dancers), coupled with severe caloric restriction and a poor calcium intake, is well known to result in functional hypogonadism (hypothalamic amenorrhoea) and osteoporosis, not infrequently associated with fracture.[268] For subjects with established disease and known vertebral fractures, weight-bearing exercise (particularly jogging) would be inappropriate, whereas for frail, elderly people already at high risk of fracture, prevention of falls is of paramount importance. Although exercise cannot be viewed as a panacea for preventing bone fragility and fracture, it remains the only non-pharmacological measure to stimulate bone formation.

10.1.3 Limit alcohol consumption and stop smoking

The deleterious effects of alcohol and smoking on bone have been discussed in some detail before (see 7.1.6 and 7.1.7). Chronic alcohol consumption, at a dose of three or more units per day, directly inhibits osteoblastic bone formation and may also cause hypogonadism, hypercortisolaemia, liver disease and hypovitaminosis D.[125-132] When alcohol abuse is suspected, it is important to ensure that an element of osteomalacia is not present. Smoking is a risk factor that is, in part, dependent on BMD.[133-135]

10.1.4 Avoid bone-toxic drugs

A number of drugs, other than alcohol and smoking, predispose to fracture, either by reducing bone strength and/or by predisposing to a fall (Table VII). Note that drugs like the anticonvulsants (which promote the catabolism of 25OHD) may cause not only osteoporosis, but also osteomalacia.

Table VII: Drugs associated with an increased risk of osteoporosis and fracture

Increased risk of osteoporosis
Glucocorticoids
Excessive thyroid replacement therapy
Anticonvulsants[a]
Thiazolidinediones (pioglitazone, rosiglitazone)
Aromatase inhibitors
Gonadotrophin-releasing hormone analogues
Chemotherapy[a]
Immunosuppressives (cyclosporine, methotrexate)
Heparin/warfarin
Chronic lithium therapy
Prolonged parenteral nutrition
Aluminium[a]
Increased risk of falling
Sedatives and hypnotics
Antidepressants
Antihypertensive drugs
Hypoglycaemic agents

[a] May also cause osteomalacia

10.1.4.1 Glucocorticoid-induced osteoporosis

Chronic (longer than three months) glucocorticoid use is a major risk factor for the development of osteoporosis.[145-150] Early on, bone resorption is stimulated, but later a marked suppression of bone formation (and resorption) results in predominantly low-turnover osteoporosis. Bone resorption is stimulated by both direct (↑RANKL/↓OPG) and indirect effects (↓ intestinal absorption of calcium and ↑ renal calcium wasting → negative calcium balance → PTH-mediated bone resorption). Glucocorticoids cause a direct inhibition of osteoblastic bone formation by suppressing the proliferation and differentiation of preosteoblasts, by stimulating their transdifferentiation to adipocytes, and by stimulating the apoptosis of mature osteoblasts and osteocytes. Additionally, glucocorticoids decrease circulating sex hormone levels (via ↓ LH, as well as direct effects on the ovaries) and may

cause a myopathy, which predisposes to falls. Glucocorticoids may also cause avascular necrosis of the hip.

Unlike involutional (age-related) osteoporosis, glucocorticoid-induced osteoporosis (GIOP) develops very rapidly. About 50% of the total bone loss occurs within the first six to 12 months of steroid treatment. If prophylactic therapy is to be of value it should, therefore, be initiated early and preferably concomitantly with the steroid treatment. Since glucocorticoids not only decrease BMD, but also adversely influence bone quality, fractures tend to occur at a higher BMD than in subjects with primary osteoporosis. It has, therefore, been suggested that pharmacological intervention should be contemplated with T-scores around -1.5 to -2.0.[149,150,269] It is often stated that bone loss occurs with a prednisone dose of ≥ 7.5 mg per day.[3] While this is correct, a clear dose response should not be assumed. Bone loss only occurs in about 50% of steroid-treated individuals, regardless of the dose. However, significant bone loss may also occur with much lower doses, and a marked individual sensitivity to the bone-toxic effects of glucocorticoids is well documented. Children and postmenopausal women are thought to be at particular risk, but men and younger women are often affected. Trabecular bone (e.g. spine) is predominantly involved, but cortical bone is not spared. Often, the very disease for which steroids have been prescribed (e.g. rheumatoid arthritis) is a risk factor for osteoporosis. Although unnecessary corticosteroids should always be avoided, steroid therapy should never be withheld if indicated.

Traditionally, calcium and vitamin D have been recommended as preventive measures for GIOP, but their role as monotherapy has always been questioned.[270] A Cochrane review, which assessed five RCTs, concluded that calcium and vitamin D significantly increase lumbar BMD, although femoral BMD and fracture incidence remain unaltered.[271] Hormone therapy (HT) has also been shown to have bone-sparing effects but, during the past decade, the aminobisphosphonates alendronate and risedronate have established themselves as first-line therapy, and generally reduce the vertebral fracture rate by about 70%.[272] Recently, treatment with zoledronic acid was shown to result in a significantly greater increase in both spine and hip BMD than risedronate in a head-to-head comparative study of glucocorticoid-treated patients, although no difference in fracture risk was documented.[273] Alendronate and the anabolic agent teriparatide were also compared in a head-to-head study in men and women with GIOP. Teriparatide therapy resulted in significantly greater increases in spine and hip BMD, and significantly fewer vertebral fractures.[274] The dual-action drug strontium ranelate, which stimulates bone formation and inhibits resorption, would appear to be ideally suited for the treatment of GIOP, but studies to assess its efficacy are still underway.

10.2 Prevention of falls

Each year, one in three people over the age of 65 years experience at least one fall, with 10–30% of falls requiring a hospital visit and 5-6% resulting in a fracture. Institutionalised

patients are particularly at risk of falling.[275] Table VIII summarises risk factors for falling. A number of systematic literature reviews have revealed that a relatively small number of risk factors for falls emerge consistently: medication, in particular sedatives, hypnotics and benzodiazepines; cognitive dysfunction; gait and balance disorders; weakness and immobility; or a history of falls will individually increase risk between two- and fivefold.[275-283]

Simple risk assessment tools, consisting of similar variables, have been shown to predict falls with sensitivity and specificity in excess of 70%.[275,279-282] A recent study, comparing the ability of eight functional mobility and balance tests to prospectively predict falls, concluded that the simple sit-to-stand test with five repeats (STS-5), the alternate-step test (AST) and the six-minute-walk test (SMWT) were the best tests.[280] Both the American and British Geriatric Society guidelines recommend the Timed Up and Go Test (TUGT), also known as the "get-up-and-go" test, as a screening tool for identifying older people at increased risk of falls.[281] The TUGT measures the time required for a person to rise from a 46 cm high chair, walk three metres at usual walking pace, turn 180^0, return to the chair and sit down. Various cut-points have been proposed to differentiate between non-fallers and recurrent fallers. Some have advocated 10 seconds[284] and others 20 seconds,[285] but 15 seconds to complete the task appears to be the best validated to discriminate between those at high and low risk of falling.[281]

Table VIII: Risk factors for falling

Institutionalisation

Mental impairment

- Dementia, confusion
- Medication (sedatives, hypnotics, tranquilisers, antihistamines, anticonvulsants)
- Severe depression (including antidepressants)
- Alcohol

Gait and balance disorders

- Postural hypotension (including antihypertensive drugs)
- Medication
- Carotid hypersensitivity
- Vestibular and proprioceptive disorders
- Neuropathies, foot disorders
- Previous stroke

Weakness and immobility

- Muscle weakness (sarcopenia)
- Impaired mobility
- Leaves home less than three times per week

Visual impairment

- Reduced visual acuity
- Reduced depth perception
- Abnormal dark adaptation

Environmental hazards and accidents

Prior falls

- More than three falls in last year
- Sideways fall(s)
- Previous fall(s) with injury

10.2.1 Assessment

The emphasis should centre on reversible causes of falls. The following should be considered:

(i) ***Medication,*** particularly long-acting sedatives, major tranquillisers and hypnotics (including non-prescription medicines like cough mixtures, which often contain antihistamines), is the single most important reversible risk factor for falls in the elderly.[275,283,286] Antidepressants, antihypertensive drugs, hypoglycaemic agents, laxatives and alcohol may also predispose.

(ii) ***Cognition and affect.*** A simple Abbreviated Mental Test (AMT or "mini mental" test)[287] and depression score are more than adequate as screening procedures.

(iii) ***Gait and balance.*** The TUGT with a 15-second cut-point is usually sufficient, although sophisticated sway meters can accurately assess body sway.[288] Further assessment of proprioception, vestibular disorders, neuropathies or local foot disorders may be required as indicated.

(iv) ***Cardiovascular examination.*** This should include assessment for postural hypotension (reduction in blood pressure of ≥ 20 mmHg when standing, compared with sitting or lying) and cardio-inhibitory carotid sinus hypersensitivity.

(v) ***Weakness and immobility.*** Melton has emphasised the fact that nearly half of all hip fracture victims have some degree of muscle weakness. He coined the term *"sarcopenia"* to underscore this important risk factor many years ago. Quadriceps strength is usually measured isometrically in the dominant leg, with the angles of the hip and knee at 90^0, and with the patient seated.[288]

(vi) ***Visual acuity*** (Snellen chart) and ***depth perception.***

(vii) ***Environmental safety.*** Up to 40% of falls are accident- or environment-related. The vast majority occur in the home during daily activities. The most important environmental risk factors are objects that may be tripped over, slippery surfaces, inappropriate furniture and poor lighting.

Previous falls. Any fall will enhance the fear of subsequent falls, resulting in loss of confidence, a reduction in activity, muscle strength and postural control, and a further increase in the risk of falling. Since < 5% of falls in elderly people result in hip fractures, the *severity* and *type* of fall, over and above mere *frequency,* appear to be important determinants of fracture risk.[276,289] *Sideways falls* are thought to increase fracture risk some 30 times more than a forwards or backwards fall. One in four falls directly on the greater trochanter is said to result in fracture.[290] The extent of a patient's soft tissue protection over the greater trochanter may further influence the amount of energy absorbed during a fall, and hence limit fractures. External hip protectors can reduce hip fracture

risk by as much as 50%, particularly in the frail and elderly with significant hip osteopenia, but require a highly motivated patient who is prepared to wear the protector at all times. Moreover, use of hip protectors has not been demonstrated to significantly reduce the risk of hip fracture in non–institutionalised elderly subjects, even when they are compliant. Hip protectors are very expensive, not readily available in this country and generally of little practical use.

10.2.2 Efficacy of fall prevention programmes

Early uncontrolled studies reported the beneficial effect of interventions which addressed the known risk factors for falls in the elderly, but a number of subsequent controlled trials failed to show efficacy.[291,292] These reports contrast with other RCTs, including the PROFET study, which showed a striking 67% reduction (OR 0.33, 95% CI 0.16-0.68) in falls.[293,294] Moreover, a recent Cochrane review of 111 trials (55,000 participants) concluded that assessment and multifactorial intervention reduced the rate of falls, on average, by 25%.[295] Home safety interventions were effective in subjects with severe visual impairment (OR 0.42, 95% CI 0.22-0.78), while gradual withdrawal of psychotropic medication significantly reduced rate of falls (OR 0.34, 95% CI 0.16–0.73). Another Cochrane review also documented a significant reduction in fall-related injuries following population-based interventions in older people.[296] Vitamin D supplementation has been shown to improve muscle strength and fall propensity, even when serum biochemistry is unremarkable and not suggestive of osteomalacia. A recent meta-analysis of RCTs concluded that 700–1,000 IU vitamin D per day reduced the risk of falling by approximately 20%.[297] Doses of less than 700 IU per day (serum 25OHD concentrations below 25 ng/ml) may not reduce the risk of falling in the elderly.

A number of earlier epidemiologic studies suggested that HT may reduce fractures by improving muscle strength, balance, reaction time and fall prevention, in addition to the well-documented prevention of bone loss.[298,299] In the WHI, a randomised study of 16,608 postmenopausal women, subjects who received estrogen plus progesterone reported statistically significant but not clinically meaningful improvement in physical function at one year, but not at three years.[300] In a recent RCT, specifically designed to assess the effects of HT on physical performance in community-dwelling elderly women, HT was again shown to have no significant effect on balance, cognition, physical measures of mobility or fall propensity.[301]

10.3 NOFSA recommendations on the non-pharmacological management of patients with osteoporosis

NOFSA recommendations

a. ***Adequate intake of calcium (1,000-1,200 mg/day) and vitamin D (800-1,000 IU/day)*** should be ensured in order to prevent secondary hyperparathyroidism, high-turnover osteoporosis (± osteomalacia), myopathy and falls. Although every effort should be made to obtain this from the diet (low-fat dairy), it is often not possible (food fortification is rare in this country and ample ultraviolet exposure is often difficult to achieve) and supplementation is, therefore, required (GRADE 1/ØØØO).

b. ***Additional vitamin D is required during pregnancy and lactation.*** It is suggested that at least 2,000 IU vitamin D per day is necessary during pregnancy and lactation (GRADE 1/ØØØO). Cholecalciferol and ergocalciferol are equipotent and either may be used as supplement.[238]

c. ***Serum 25OHD levels should be routinely monitored,*** particularly in those subjects where vitamin D deficiency is likely to be present, viz elderly institutionalised, sun-protected (religious reasons, sun screens), dark-skinned, obese, or malnourished individuals (GRADE 1/ØØOO). No consensus exists as to whether the aim is for 25OHD serum levels of 20 or 30 ng/ml (see 9.1). A number of studies have suggested that PTH secretion starts to increase with 25OHD levels below 30 ng/ml.[302-304] A lower level of 25OHD has been suggested by a large Dutch study,[305] but this may have been influenced by high calcium intake in the population, which suppresses PTH and influences the serum 25OHD at which secondary hyperparathyroidism becomes manifest.[219] Moreover, given reports[213,214,216-221] that as little as 16-18% of the general population in the UK aged over 65 years have 25OHD levels in excess of 30 ng/ml, and that this value may fall to as low as 4% in hip fracture cases, it is recommended that, until more local data become available, we use Michael Holick's classification.[210,211] According to this classification, a serum 25OHD level > 30 ng/ml indicates a vitamin D-replete state, level < 20 ng/ml suggests vitamin D deficiency, and levels between 21 and 29 ng/ml reflect relative vitamin D insufficiency (GRADE 1/ØØOO). Patients with vitamin D deficiency osteomalacia invariably have 25OHD levels of 5-10 ng/ml. Remember that, in the long-term, for every 100 IU vitamin D ingested daily, the serum 25OHD increases by approximately 1 ng/ml.[211,237,238]

d. ***Monitor urine calcium excretion*** in subjects on high doses of vitamin D, or those with a previous history of kidney stones (GRADE 1/ØØOO).

e. ***Walking for 5 km at a brisk pace, three to four times per week,*** is recommended to improve hip bone strength, while ***back-strengthening***

exercises will improve vertebral bone strength. In the elderly, particularly, the involvement of a professional physiotherapist should be considered (GRADE 1/ØØOO).

f. ***Stop smoking and limit alcohol to less than three units per day*** (GRADE 1/ØØOO).

g. ***Prevent falls by assessment of:***

(i) ***Medication:*** Particularly sedatives/tranquilisers; attempt to reduce or withdraw.

(ii) ***Cognition and affect:*** Mini mental test and depression score, then treat as indicated.

(iii) ***Gait and balance:*** Do a "get-up-and-go" test as a screening test.

(iv) ***Weakness and mobility:*** Check quadriceps strength; initiate exercise programme.

(v) ***Cardiovascular examination:*** Should include assessment for postural hypotension (reduction in blood pressure of ≥ 20 mmHg when standing, compared with sitting and reading) and cardio-inhibitory carotid sinus hypersensitivity.

(vi) ***Visual acuity/depth perception:*** Consider referral to ophthalmologist.

(vii) ***Environmental safety:*** Make the home a fall-safe area (GRADE 1/ØØOO).

A practical algorithm for the clinical assessment of falls is presented in Figure 6, where the "get-up-and-go" test is largely used as screening test for gait and balance abnormalities. Subjects with abnormalities of gait and balance and/or recurrent falls should be subjected to a ***multifactorial fall management programme***, which includes a full assessment of *(i)* - *(vii)* above.

h. ***Avoid bone-toxic drugs,*** which could possibly cause osteoporosis, and also consider osteomalacia when certain drugs are used (Table VII).
Glucocorticoid–induced osteoporosis (GIOP) should be prevented and managed by attending to the following:

- Use the lowest effective dose of glucocorticoid possible, taking due cognisance of marked individual sensitivity and the fact that no dose is safe (GRADE 1/ØØØO).
- Alternate-day regimens and high-dose inhaled steroids are also associated with bone loss (GRADE 1/ØØØO).
- Preventive measures should be implemented early. A baseline bone mass measurement, sex hormone levels (in premenopausal women, and men) and a urinary calcium level should be obtained in all patients in whom

long-term (longer than three months) glucocorticoid treatment is contemplated (GRADE 1/ØØOO).

- Hypogonadism (hormone replacement therapy) and hypercalciuria (indapamide or thiazides) should be treated, if present (GRADE 1/ØØOO).
- An adequate calcium and vitamin D intake must be ensured, although the value of monotherapy remains uncertain (GRADE 1/ØØOO).

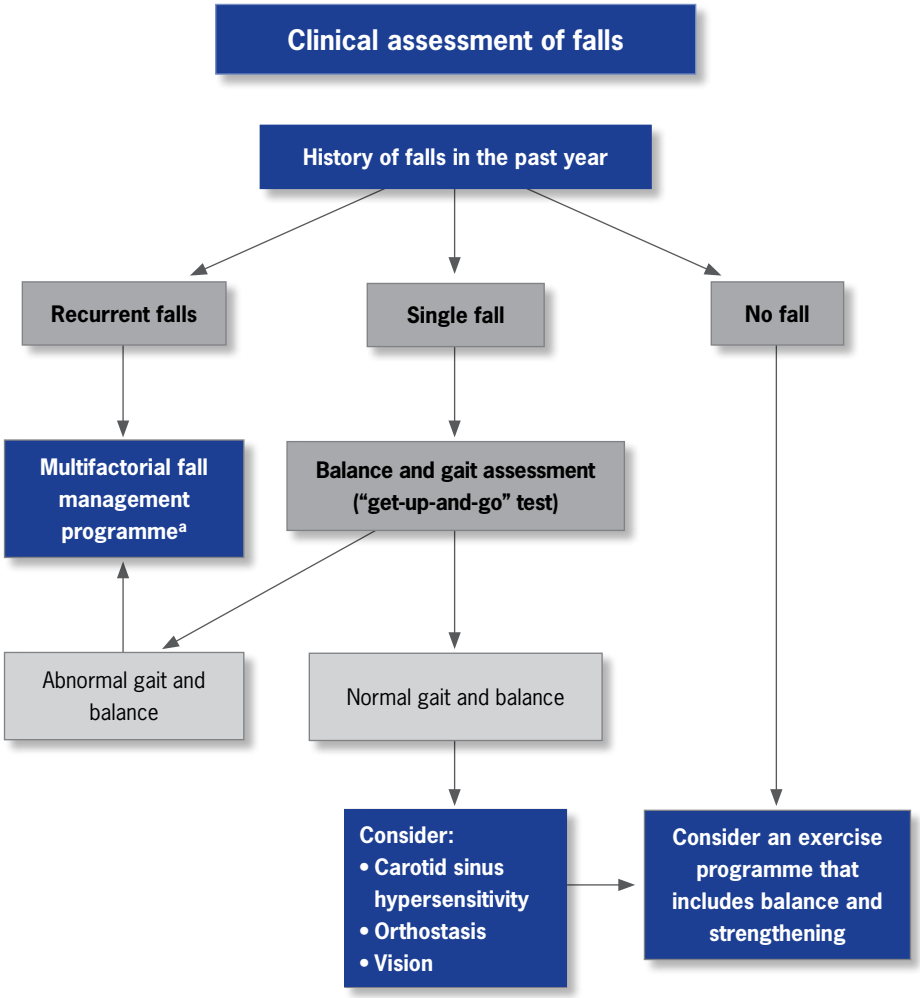


Figure 6: Algorithm for the assessment of falls

[a] See 10.3 for details

NOFSA recommendations

- We do not recommend that all patients on chronic glucocorticoid treatment be treated with a bone-active agent (other than calcium/vitamin D), a policy advocated by a number of rheumatological societies abroad. Since only 50% of patients on long-term glucocorticoids will develop GIOP, regardless of the dose, we recommend that a BMD measurement be obtained in all patients. If the BMD T- or Z-score is ≤ -1.5, treatment with a bone-active drug should be considered. This is particularly relevant if other clinical risk factors (CRFs) for the development of osteoporosis (see 7.1) are present. If the BMD T- or Z-score is ≥ -1.5 and other risk factors are absent, a more conservative approach may be adopted with calcium, vitamin D, an exercise programme and a *repeat BMD in six months*, following which treatment options can be reassessed (GRADE 1/ØOOO).
- Bisphosphonates have proven to be effective in GIOP, and comprise first-line therapy (GRADE 1/ØØØO).
- Anabolic agents do not have a role in prevention, but should be considered in chronic cases (where turnover is usually suppressed) and in advanced disease (where BMD is very low or fractures are present) (GRADE 1/ ØØOO).
- Monitoring the response to therapy in osteoporosis is problematic at best, and poses a particular problem in GIOP, since some patients will never develop the disease and others may develop it after relative short or low-dose exposure. Unlike involutional osteoporosis, it is suggested that a follow-up BMD measurement, utilising central DXA, be obtained *within one year of initiating glucocorticoid treatment* (GRADE 1/ØØØO).

11 Pharmacotherapy of osteoporosis

The pharmacological agents currently used in the management of osteoporosis include:

- Drugs which specifically aim to prevent bone loss, improve bone strength and reduce the risk of future fractures (i.e. specific therapeutic agents).
- Drugs which reduce the pain and disability associated with a fracture.

The administration of specific therapeutic agents will not result in short-term symptomatic pain relief, and vice versa. Although exceptions to this rule may exist (see 13.4), this must be explained to patients if long-term compliance is to be ensured. Specific therapeutic agents used in osteoporosis are usually classified as inhibitors of bone resorption (anticatabolics), stimulators of bone formation (anabolics), or dual action agents (Table IX).

Table IX: Drugs currently used to treat osteoporosis

Inhibitors of bone resorption: anticatabolics	
Calcium/vitamin D Estrogen/progestins Estrogen analogues, selective estrogen receptor modulators (SERMS), testosterone • raloxifene • tibolone • phyto-estrogens • testosterone	Bisphosphonates • alendronate • risedronate • zoledronate • pamidronate • ibandronate Calcitonins
Stimulators of bone formation: anabolics	
Parathyroid hormone	Fluoride
Drugs with dual or complex actions on bone	
Strontium ranelate Vitamin D metabolites (calcitriol/alfacalcidol)	Anabolic steroids Thiazide diuretics/indapamide

Bone is a dynamic tissue, continuously engaged in maintenance remodelling. At any point in time, some bone will have been resorbed, but not yet replaced. This is referred to as the *remodelling space,* and is increased in osteoporosis. Antiresorptive agents (ARAs) decrease the rate of initiation of new remodelling cycles, resulting in fewer remodelling sites and a decrease in the remodelling space. ARAs aim to stabilise bone mineral density (BMD) and prevent further loss of bone. After initiating treatment with ARAs, bone resorption rapidly decreases while formation continues, resulting in the filling in of the remodelling space and a modest (2-8%) increase in BMD over this time. Coupling between resorption and formation, however, results in a subsequent decrease in the rate of formation and, after two to three years, bone mass usually stabilises for the duration of treatment (Figure 7). ARAs, like the bisphosphonates and estrogen, do not only decrease the rate of bone loss, but also decrease the depth of resorption cavities and, therefore, improve bone quality. Only drugs which directly stimulate bone formation can, however, be expected to result in a sustained increase in BMD and correction of microarchitecture.

Adapted from Parfitt[306] and Eastell[307]

Figure 7: Effects on BMD after treatment with ARAs and bone formation-stimulating drugs

The choice of a specific agent to treat osteoporosis is made difficult by the lack of head-to-head studies comparing the efficacy and safety of different agents. No "best drug" scenario therefore exists, and the choice of drug usually has to take into account the patient profile (age, gender, general health), the nature of the disease (cause, severity, skeletal sites involved) and the availability and side-effects of specific drugs.

11.1 Inhibitors of bone resorption

Inhibition of bone resorption can be effected by manipulation of (i) osteoclast formation, (ii) activity of mature osteoclasts, and (iii) osteoclast apoptosis. Currently available ARAs include calcium/vitamin D, estrogens and selective estrogen receptor modulators (SERMS) which largely, although not exclusively, suppress osteoclastogenesis, and the bisphosphonates and calcitonins, which inhibit osteoclast activity and promote osteoclast apoptosis. Improved understanding of osteoclast biology has recently uncovered a number of novel targets for controlling osteoclast formation and activity. Since some of these new drugs will be launched within the next year or two, it is appropriate to mention them here, although any discussion of these agents falls outside the scope of this guideline. Some of these newly developed drugs include inhibitors of the RANKL pathway, like the monoclonal antibody denosumab, which inhibits osteoclastogenesis and has already been shown to increase BMD and to reduce fracture risk.[308] Inhibitors of osteoclast activity include the cathepsin K protease inhibitor odanacatib, inhibitors of carbonic anhydrase (CA2), osteoclast integrins, vacuolar H^+-ATPase, and various signalling pathways (p38 kinase, $p60^{C\text{-}SRC}$ kinase), as well as glucagon-like peptide 2 which inhibits the circadian nocturnal rise in bone resorption.[309-311]

11.1.1 Calcium and vitamin D

The more common causes of calcium and vitamin D deficiency (see 7.1.9), the assessment of calcium and vitamin D (measured as 25OHD) status (see 9.1), and the effects of calcium and vitamin D on peak bone mass, age-related bone loss and fracture risk (see 10.1.1.1) have been discussed in some detail. We shall now briefly comment on pharmacological supplementation of calcium and vitamin D.

11.1.1.1 Calcium supplementation

The amount of calcium required to attenuate bone loss is unknown, although a total daily intake of 1,000-1,200mg of *elemental* calcium is usually recommended (Table VI). This dose should, however, be individualised and may have to be increased if dietary habits reflect poor intake or suggest low bioavailability (excess sodium, protein, fibre, drugs). It is important to remember that, when supplements are used, the yield of *elemental* calcium varies with the calcium salt employed (Table X). Calcium carbonate preparations should be

taken with meals, since HCl is required to liberate free calcium and improve its intestinal absorption. Although differences have been reported in the bioavailability of calcium between proprietary preparations, these are usually small and probably not clinically significant. An average dose of 500 mg elemental calcium per day is usually sufficient. If concomitant deficiencies in vitamin D (see 7.1.9) or magnesium (e.g. alcoholism, diabetes, malabsorption syndromes, use of diuretics), known to impair calcium bioavailability, are present, they should be supplemented. The *routine* supplementation of magnesium, either alone or in combination, is not recommended. Calcium is easy to use and generally well tolerated, although patient compliance is often poor because of gastrointestinal side-effects, particularly constipation.

Table X: Elemental calcium content of commonly used calcium supplements

Calcium salt	***Yield of elemental calcium***
Calcium carbonate	40%
Tribasic calcium phosphate	38%
Calcium chloride	27%
Dolomite	22%
Calcium citrate	21%
Calcium lactate	13%
Calcium gluconate	9%

Safety of calcium supplements. Calcium supplementation may cause gastrointestinal symptoms and is associated with a small (10-15%) increase in renal stone disease, but is generally regarded as quite safe. Recently, however, Bolland et al reported an increased risk of cardiovascular disease in postmenopausal women taking calcium supplements, and followed this up with a meta-analysis of 11 RCTs which documented a 27% increase in cardiovascular diseases in women taking calcium supplements.[260] Mortality and the incidence of stroke were not increased. This study is to be contrasted with the large WHI which clearly showed that calcium, taken with low-dose Vitamin D, was not associated with an increase in cardiovascular disease. An adequate calcium intake is also thought to be associated with a reduction in cardiovascular disease risk factors, like hypertension and hypercholesterolaemia. Moreover, calcium is always a mandatory component of drug trials which assess the effects of potent anti-fracture medication, and these studies have generally been associated with a reduction in all-cause mortality.

The reasons for these discrepancies remain unclear, but they may be a function of the calcium dose employed. The Bolland study selected RCTs with an exceptionally high dose of supplemental calcium, the average dose being 1,200 mg/day and a number of studies included in the meta-analysis using doses of 1,500–2,000 mg/day. Furthermore, the

dietary calcium intake in these subjects was above average (900 mg/day), and a positive correlation was found between the proposed increase in cardiovascular disease and the dietary intake of calcium. In fact, the *increase in cardiovascular disease was entirely limited to those with a calcium intake of more than 800 mg/day.* Whereas there is little evidence to suggest that calcium supplementation in doses ≤ 500 mg/day is harmful, high-dose calcium supplementation in patients already consuming ample dairy, particularly those with renal impairment or known cardiovascular disease, is unnecessary and best avoided.

11.1.1.2 Vitamin D supplementation

Parfitt has defined three degrees of hypovitaminosis D osteopathy.[312] *Stage 1* is characterised by diminished intestinal calcium absorption, which results in osteoporosis without histologic changes of the skeleton; *stage 2*, by impaired calcium absorption and osteoporosis, plus early histologic features of osteomalacia without any biochemical abnormalities suggestive of osteomalacia; and *stage 3*, by clinical and laboratory features of osteomalacia. Prophylactic doses of vitamin D range from 800-1,000 IU per day, and either cholecalciferol or ergocalciferol may be used (see 10.1.1.1). If serum 25OHD levels indicate relative vitamin D insufficiency (< 30 ng/ml), serum PTH levels and bone turnover start to increase, high-turnover osteoporosis develops, and treatment with larger doses of vitamin D (e.g. 50,000 IU every two to four weeks) should be considered. Circulating 25OHD levels > 10 ng/ml appear quite adequate to prevent osteomalacia from developing, whereas levels below 5-8 ng/ml are usually accompanied by a mineralisation defect. If osteomalacia is present, treatment with 50,000 IU per week is indicated. There are no indications for or advantages to using one of the more potent vitamin D metabolites or analogues for treating simple nutritional vitamin D deficiency, although these agents should be considered if the vitamin D deficiency has resulted from intestinal malabsorption.[313] When larger doses of vitamin D are given, monitoring of urinary calcium is usually recommended, although intakes of up to 4,000 IU per day have been shown to be well tolerated without abnormal increases in serum or urine calcium.[247,314,315]

11.1.2 Hormone therapy

In this guideline, the term "hormone therapy" (HT) is used generically to denote the use of estrogen ± progestin in postmenopausal women. Estrogen alone is referred to as ET, and estrogen in combination with progestogen as EPT. In this guideline, "hormone replacement therapy" (HRT) will be reserved for true estrogen/progestogen replacement in hypogonadal, premenopausal females.

Until 2002, HT was regarded as first-line therapy for the prevention and treatment of postmenopausal osteoporosis. Not only was HT thought to be highly effective in combating the symptoms of the menopause, but numerous observational studies suggested that it

also significantly reduced the risk of CHD by 30-50%, and that of cerebrovascular accidents by 15-20%.[316-319] It was, therefore, reasoned that any risks associated with HT were far outweighed by these extraskeletal benefits. However, in 1998, the first RCT of oestrogen plus progestin for secondary prevention of CHD in postmenopausal women (the HERS study) not only failed to document a protective effect, but reported a significantly *higher* rate of CHD events during the first year of HT.[320] In 2002, the first results of the WHI were published, confirming a beneficial effect of HT on fracture prevention, but failing to show any benefits of HT on CHD and, in fact, reporting a 29% increase in the risk of non-fatal CHD events, although this did not reach statistical significance.[321] The risk of stroke was also increased and this did reach nominal, but not adjusted, statistical significance. These observations resulted in regulatory bodies like the American Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) advising against the use of HT as first-line therapy for the management of osteoporosis. During the past eight years, much debate, reassessment of data and some new information have provided new insights which will be summarised here, since the subject has been extensively reviewed, both internationally[322-324] and locally.[325,326]

11.1.2.1 Effects of hormone therapy on bone

Numerous observational and controlled studies have provided evidence of a beneficial effect of HT on BMD and vertebral fracture risk, but we had to wait for the WHI to convincingly document a reduction in the rate of hip fractures.

Bone mineral density. HT has consistently been shown to increase BMD at all major skeletal sites.[327-332] In 2001, a meta-analysis of 57 RCTs found an average increase of BMD of 6.8% at the spine and 4.1% at the femoral neck after two years of HT.[329] Similar data were reported in the PEPI[330] and NORA[331] studies, and the WHI.[332] The response is dose related, and a daily dose of 0.625 mg conjugated equine estrogen (CE) (equivalents are 2 mg estradiol valerate; 1 mg micronised 17-β-estradiol; 50 µg estradiol transdermally) is required for an optimal effect. Higher doses do not appear to result in an improvement, although unconfirmed reports have suggested that higher doses may have an anabolic effect on bone and may be required if predominantly cortical osteopenia is treated. Given the extraskeletal side-effects of HT (see below), much interest resides in the effects of low-dose HT on bone. RCTs using half the conventional HT dose (oral 0.3 mg CE per day; oral 0.5 mg micronised 17-β-estradiol per day; transdermal 25 µg estradiol per day) have shown significant increases in both spine (2-4.7%) and hip (1-3.6%) BMD.[333-335] In fact, an ultra-low oral dose of 0.25 mg micronised estradiol per day significantly suppressed biochemical markers of bone turnover and increased vertebral and hip BMD by 2-4%.[336] The beneficial effects of low-dose HT on BMD appear to be most pronounced when ample calcium and vitamin D is supplied, and an additive effect of these agents on bone resorption has been suggested.[333,334] Optimal vitamin D repletion has also recently been shown to

augment the BMD and anti-fracture efficacy of the bisphosphonates and raloxifene, and seems to be necessary to maximise the bone effects of most ARAs.[337] Significant lumbar spine and hip BMD improvements have also been noted with systemic estrogen doses delivered via a vaginal ring (Femring®, Menoring®).[338]

The route of administration (tablet, skin implant, patch, gel or nasal spray) appears to be relatively unimportant as far as bone is concerned, but impacts significantly on the extraskeletal effects of HT (see below). The bone-sparing effect of estrogen persists as long as therapy is given. It is most pronounced during the first five to 10 years after the menopause. Some evidence suggests that catch-up bone loss occurs after HT has been discontinued, while other studies show that the rate of bone loss after HT is stopped is similar to the rate immediately before therapy was instituted. Although the PERF study[339] suggested that two to three years of HT have long-term protective effects on bone loss and osteoporotic fractures, the larger NORA[331] and Million Women Study[340] strongly supported the contention that bone is rapidly lost once HT is discontinued. If bone protection is required at this stage, the addition of a bisphosphonate or other bone-active drug is, therefore, recommended.[341,342] Similar to other ARAs, HT often results in a modest transient increase in BMD. This can be ascribed to filling in of the remodelling space (Figure 5), is more evident if pretreatment bone turnover is high,[171] and is usually not sustained beyond two to three years. Not all patients respond to HT and some 10-20% of subjects lose bone at conventional doses of estrogen. It is unclear whether this is the result of poor adherence to treatment or inherent resistance to the action of the hormone. The antiresorptive mechanism of action of estrogens (largely inhibition of osteoclastogenesis) differs from that of the bisphosphonates (predominantly suppression of osteoclast activity), and preliminary studies have suggested additive effects on bone markers and BMD when these agents are used in combination.[343,344] No data on fracture risk are, however, available.

When EPT is given, the choice of progestin may also influence the skeletal response. Progestins which possess greater androgenic and lesser glucocorticoid activity (e.g. norethisterone acetate, NETA) have been shown to exibit superior protection against bone loss as well as fracture, compared with progestins with less androgenic or more glucocorticoid activity (e.g. medroxyprogesterone acetate, MPA).[345] Further studies are, however, required to confirm this observation, which has been refuted by some.[340] No current evidence supports the contention that progestins alone improve BMD or decrease fracture risk.

Fractures. Prior to the publication of the WHI results in 2002, evidence from observational studies and some RCTs indicated that standard–dose HT reduced the risk of osteoporotic fractures.[327-329,346-350] Evidence was convincing for a reduction in the risk of vertebral fractures, but less so for hip fracture, although two meta-analyses of RCTs did report a reduction in non-vertebral fractures of 27%.[316,351] The WHI was, however, the landmark

study which unequivocally proved that both ET and EPT reduced the risk of spine, hip and total fractures by 24–39%.[321,332,352] Subsequently, these results were corroborated by two large observational studies: NORA, which is a longitudinal follow-up study of 200,160 postmenopausal women,[331] and the Million Women Study, a prospective observational study of 138,737 postmenopausal females.[340]

The large WHI (n = 26,600) study was unique in a number of ways, and redefined the role of HT in the management of osteoporosis. It was not only the first RCT to unequivocally prove that HT reduced the risk of all major osteoporotic fractures but, unlike other osteoporosis trials, patients were unselected and not at high fracture risk. Most patients did not have a BMD in the osteoporosis range, yet HT also proved to be effective in those subjects with osteopenia. Furthermore, study outcomes did not include spine X-rays, so that the effects of HT on radiological fractures were undoubtedly underestimated. We have previously taken cognisance of the fact that lower doses of HT improve BMD and suppress biochemical markers of bone turnover. Unfortunately, no study to date has yielded data to support the theory that low-dose HT affords protection against fractures.

11.1.2.2 Non-skeletal effects of hormone therapy

The therapeutic envelope of any intervention is defined by the ratio of benefit to risk. The WHI report clearly highlighted the major benefits of HT for bone health and fracture prevention.

The non-skeletal effects of HT, derived from the WHI and other studies,[316,320-326,330,331,353] can be tabulated as follows:

- Systemic HT is the only treatment which has been consistently shown to be superior to placebo in the treatment of ***vasomotor symptoms*** and the associated sleep disorders that attend the early menopause.
- Systemic or local HT is effective in the management of ***vulval and vaginal atrophy***.
- EPT is associated with a small, but significant, increase in the risk of invasive ***breast cancer*** if used for longer than seven years. Although the RR is in the order of 1.35, the absolute increase in risk is small (less than 0.1% per year). ET does not increase the risk of breast cancer and may, in fact, reduce such risk.
- The risk of ***venous thromboembolism (VTE)*** is doubled with HT. The effect is maximal in the first year of treatment and more pronounced with advancing age, obesity, and previous VTE. The absolute risk of VTE in the age group 50–60 years is very small (approximately 2/1,000 per year). Nonetheless, it would seem prudent not to recommend HT in patients with spontaneous thrombosis, particularly those occurring during pregnancy or whilst taking the estrogen contraceptive pill, unless abnormalities of coagulation and fibrinolysis have been excluded. It is also advisable to discontinue HT temporarily during surgery or immobilisation (including air travel).

- The WHI study failed to demonstrate a reduced ***risk of CHD*** in HT users. In the EPT arm, a non-significant increase (7/10,000 women per year) in non-fatal CHD was, in fact, found. The WHI study subjects were relatively old (average age 64 years) and not screened for CHD risk factors. Recently, the "therapeutic window" hypothesis has evolved, which attempts to accommodate the disparate observations that HT may be protective against CHD under certain circumstances, yet may exacerbate the risk of CHD in other circumstances. According to this hypothesis, which is supported by substantial basic and epidemiological data, estrogen may offer protection when the arterial endothelium is still healthy and intact. In elderly women with established vascular disease, estrogen may, however, destabilise an atherosclerotic plaque and precipitate an event. Data from the ET arm of the WHI have documented a significant trend (p = 0.02) for CHD events to be lower the shorter the period since the menopause, as well as in younger individuals.[354] Even more encouraging results have emerged from a recent analysis of the Nurses' Health Study[355] in women starting HT near the menopause, showing a significantly reduced risk of CHD for both women on estrogen alone (RR = 0.66; 95% CI 0.54–0.80) and for women on estrogen plus progestogen (RR = 0.72; 95% CI 0.56–0.92). A recent subanalysis of subjects in the ET arm of the WHI study, which assessed the coronary artery calcium scores (CACS) in 1,064 women aged 50-59 years, concluded that the calcified plaque burden was significantly lower in those who had been on ET.[356]
- The WHI study reported an increased ***risk of stroke*** in both ET (hazard ratio, HR, 1.39) and EPT (HR 1.39) users (significant on unadjusted, but not on adjusted values), which is consistent with results from the Nurses' Health Study. Unlike VTE, the effect was not confined to the first year of HT, but was maintained throughout the study. These results are to be contrasted with those of the Danish Nurses Study[357] which found that unopposed estradiol (1 mg per day) was not associated with an increased risk of stroke (HR 0.80; CI: 0.40–1.61) in 13,122 healthy postmenopausal women followed up for five years. It has been suggested that the effect of HT on stroke may be dose-related, with smaller doses being protective and larger doses harmful.[358]
- The risk of ***endometrial cancer*** is significantly increased (two- to fivefold) in women who use estrogen without added progestin. It is, therefore, mandatory that all women with an intact uterus who wish to use HT add a progestin to the estrogen regimen. EPT largely eliminates the increased risk, provided that the dose and schedule of progestogen therapy is adequate to prevent endometrial hyperplasia (e.g. 5 mg MPA or 2 mg NETA per day for 10 days per month; 2.5 mg MPA or 1 mg NETA per day continuously).
- The WHI study failed to demonstrate a beneficial effect of HT on ***Alzheimer's disease or dementia***. Worsening of cognitive function may, in fact, occur in patients over the age of 65 years. EPT reduces the risk of ***colorectal cancer***. In the elderly,

observational studies have suggested that HT may decrease the propensity for ***falling***, but this has not been confirmed in RCTs, including the WHI.

- Occasionally, HT-induced exacerbations of hypertension, migraine, gall bladder disease, endometriosis, porphyria, systemic lupus erythematosus or deterioration in diabetes control may occur. Melanoma has been reported to recur during pregnancy and, for this reason, HT is usually avoided. Contraindications to HT are listed in Table XI.
- "Less serious", often transient, side-effects of HT commonly occur during the first year of therapy and constitute one of the principal reasons why more than 50% of women stop taking treatment during this time. Counselling and sympathetic attention to unwelcome menstrual bleeds, breast discomfort, fluid retention, mood changes and weight gain (despite reports to the contrary) are paramount to ensure successful HT and a satisfied patient.

Table XI: Contraindications to hormone therapy[325,359]

- Current, past or suspected breast cancer
- Known or suspected estrogen–sensitive malignant tumours
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Pregnancy
- Current VTE or previous idiopathic VTE
- Known CHD
- Untreated hypertension
- Active liver disease
- Porphyria cutanea tarda
- Systemic lupus erythematosus

11.1.2.3 Therapeutic regimens

Oral preparations. In hysterectomised women, only estrogen preparations are required and this may be given continuously. In women with a uterus, combined HT (EPT) using an estrogen plus progestogen is mandatory. The following regimens may be utilised:

- *Sequentially opposed HT.* Estrogen is given for 21-28 days, and the progestogen for the last 10-14 days. Various monthly packs of an estrogen plus a progestin are also available. After the progestogen is stopped, women experience a withdrawal bleed, but obviously this does not imply a return of fertility. Unfortunately, the return of monthly periods is one of the most common reasons for non-compliance with HT.

- *Continuous combined HT.* Both estrogen and progestogen are given continuously, either individually or as a single oral preparation. Should EPT be required for more than five years, it is recommended to convert from sequential to continuous combined HT. Continuous progestogen administration requires a minimum of 2.5 mg MPA or 1 mg NETA daily to suppress endometrial proliferation and generally does not induce cyclical bleeding. Unpredictable bleeding or spotting occurs in some 25% of women during the first six months, although more than 80% of subjects have no bleeding after one year. Irregular bleeds occur more often in perimenopausal women than in women with a longer duration of menopause. Irregular bleeding may be minimised by increasing the dose of progestogen. Bleeding which persists beyond the first six months requires further gynaecological assessment.
- *Long-cycle sequentially opposed HT.* Here the progestin is given for 14 days, every three months. Less extensive data on endometrial protection are available with this regimen, and it is generally not recommended on present evidence.

Non-oral preparations. Non-oral routes of HT administration (e.g. transdermal) avoid the first-pass effect in the liver and are preferable in hypertriglyceridaemia, carbohydrate intolerance, obesity, mild liver disease, gallstones, previous DVT, and in smokers.[346,354,360]

11.1.2.4 The perimenopause

The perimenopause is generally defined as that period preceding the menopause (lasting no longer than 12 months) during which periods of oligo- or amenorrhoea are experienced. Standard HT regimens are often associated with side-effects (e.g. weight gain, irregular bleeds, mood swings) at this time. A meta-analysis of 12 studies in 1998[361] suggested that plasma and urinary estrogen levels (during both follicular and luteal phases) are, on average, significantly *higher* in perimenopausal women than young premenopausal women. BMD was shown to decrease rapidly at this time. Reasons for this bone loss, at a time when circulating estrogen levels are not decreased but are in fact quite high, remain unclear. Whereas irregular bleeds and other "menopausal" symptoms may respond to progestin therapy, appropriate measures to curb bone loss are poorly defined. Standard HT is often poorly tolerated and the estrogen-containing contraceptive pill has been suggested, unless contraindicated. Alternatively, if bone protection is required, non-hormonal bone-active agents may be considered.

In summary:

It appears that the effects of HT in elderly women and those with established CHD cannot be extrapolated to the young, healthy woman in early menopause.

HT should only be initiated for *specific, proven indications*, provided there are *no contraindications* (Table XI), and should be *individualised* according to need.

There is general consensus that HT *should be considered* in subjects (i) with premature menopause, (ii) with significant vasomotor symptoms, (iii) with symptomatic urogenital atrophy, and (iv) in the 50-60 year age group, with menopausal symptoms and an above-average risk of osteoporotic fracture (e.g. osteopenia on DXA).

There is also agreement that *HT is not indicated* (i) as universal treatment at menopause, (ii) purely as a strategy to prevent CHD, and (iii) after the age of 60 years.

There are *two major points of contention*,[326] namely (i) whether HT should be continued after the age of 60 years following appropriate initiation in subjects aged 50–60 years, and (ii) whether HT should be regarded as first-line therapy for the prevention/treatment of osteoporosis in *asymptomatic*, early postmenopausal women, as suggested by the International Menopause Society (IMS).[362]

Low-dose HT has been shown to be effective for menopausal symptom control and the prevention of bone loss, and is, therefore, generally recommended. We do, however, need to take cognisance of the fact that low-dose HT has not yet been shown to provide adequate fracture protection.

Until further evidence is available, all estrogen and progestogen preparations should probably be considered similar in terms of clinical risks and benefits. The same applies to routes of administration. *Transdermal HT* does, however, have fewer *metabolic consequences* and may be more appropriate for some women.

11.1.3 Selective estrogen receptor modulators, estrogen derivatives, phyto-estrogens, progestins and testosterone

11.1.3.1 Selective estrogen receptor modulators

SERMs, for example raloxifene, lasofoxifene or bazedoxifene, are capable of binding to the estrogen receptor (ER), resulting in estrogen agonist effects in some tissue (e.g. bone) and in estrogen antagonist effects in others (e.g. breast, endometrium).[363-373] The molecular mechanisms of action of the SERMs are complex and involve differential binding to the ER-α (selective partial agonist/antagonist effects) and ER-β (selective antagonist effects) receptors, as well as actions which directly decrease the resorptive activity (e.g. decreased production of IL-6 and TNF-α) or the number (e.g. decrease in RANKL, increased production of TGF-β_3) of osteoclasts.[368]

Raloxifene has been extensively studied and is registered in South Africa for the prevention and treatment of osteoporosis. The drug has estrogen-like effects on bone, lipids and the vasculature, although it differs from standard HT in many ways. Results from the MORE

study, a four-year RCT of 7,705 postmenopausal women, showed a very modest increase in spine (2.6%) and femoral neck (2.1%) BMD, and a moderate decrease of around 30% in the levels of biochemical markers of bone resorption.[363,364] A decrease in the rate of vertebral fractures (50%), comparable to that of potent ARAs like the bisphosphonates (see below), was, however, documented. There was no difference between raloxifene and placebo groups in the risk of non-vertebral fractures, including hip fractures. These results were corroborated in a recent RCT of more than 10,000 postmenopausal women, not selected on the basis of osteoporosis, who participated in the RUTH study.[373] A reanalysis of the MORE data further showed that raloxifene was also effective in significantly reducing the risk of vertebral fractures in subjects with osteopenia, as opposed to osteoporosis.[367] These results are similar to those obtained with HT in the WHI and in contrast to the bisphosphonate data, where osteopenic patients without fractures did not show any decrease in the risk of vertebral fractures. No data are available on the effects of SERMs on fracture risk in men.

There is also much interest in the extraskeletal effects of the SERMs. Raloxifene was shown to significantly decrease (HR 0.56; 95% CI 0.38–0.83) the risk of ER-positive invasive breast cancer.[363,370] Unlike unopposed estrogen, raloxifene does not stimulate endometrial hyperplasia and is not associated with menstrual bleeds or an increased risk of endometrial cancer. Raloxifene has favourable effects on LDL cholesterol and inflammatory markers, and improves vascular endothelial function in postmenopausal women. Although the four-year results from the MORE trial suggested a reduced risk of cardiovascular events in the subset of women with increased cardiovascular risk,[369] the definitive RUTH study showed no significant effect on the risk of primary coronary events.[370] Raloxifene was, however, associated with an increased risk of fatal stroke (HR 1.49; 95% CI: 1.0–2.24) and VTE, although the absolute risk is small (< 2 per 1,000 woman-years). Hot flushes are not suppressed by raloxifene and their incidence is, in fact, increased by this drug. Raloxifene may also cause leg cramps.

A number of new SERMs are currently being assessed in phase III trials. *Bazedoxifene* is an example of such a drug, and holds much promise. In an RCT of 6,847 postmenopausal women, this drug was not only shown to reduce vertebral fracture risk by 40%, but also caused a 44-50% reduction in non-vertebral fracture risk relative to placebo in a subset of patients at particular high fracture risk (femoral neck T-score below –3.0 and/or multiple vertebral fractures).[374] *Lasofoxifene* was recently shown to significantly reduce the rate of vertebral and non-vertebral fractures at a dose of 0.5 mg daily over five years.[365] It furthermore decreased the risk of ER-positive breast cancer, major cardiovascular events and stroke, excluding transient ischaemic attacks. The risk of endometrial cancer and hyperplasia was comparable to that of placebo, although the risk of endometrial polyps and vaginal bleeds was increased. Compared with placebo, the use of a lower dose (0.25 mg

per day) of lasofoxifene was associated with an increased mortality, but this could not be ascribed to any particular cause or event.

Tissue-selective estrogen complex (TSEC). The results of a phase III trial employing a combination of various doses of bazedoxifene and CE were recently published.[372] CE (0.45 mg or 0.625 mg per day) combined with bazedoxifene (20 mg per day) resulted in a significant improvement in BMD at the spine when compared with placebo or raloxifene, and at the hip when compared with placebo. Compared with placebo, the combination improved vasomotor symptoms and vaginal health without causing endometrial hyperplasia. The TSEC compound has the promise of replacing progestins as the endometrial protective agent used in combined HT in non-hysterectomised women. Its use in osteoporosis will be subject to fracture data. It should also be noted that these results should not be extrapolated to other SERM/estrogen combinations, since all act differently and it is possible that the other available SERMs may not adequately protect the endometrium.

11.1.3.2 Tibolone

The synthetic steroid derivative *tibolone* has mild estrogenic, progestogenic and androgenic properties, and has been defined as a selective tissue estrogenic activity regulator (STEAR). This drug reduces vasomotor symptoms, may improve mood and libido, and is effective in preventing postmenopausal bone loss.[375-377] The LIFT trial, an RCT of 4,538 postmenopausal women, revealed a significantly decreased risk of both vertebral (HR 0.55; 95% CI 0.41–0.74) and non-vertebral (HR 0.74; 95% CI 0.58-0.93) fracture.[378] The tibolone group also had a decreased risk of invasive breast cancer and colon cancer, and no significant increase in the risk of either CHD or VTE. However, the tibolone group had a highly significantly increased risk of stroke (HR 2.2; 95% CI 1.14-4.23). This drug should, therefore, not be used in women at risk of stroke. It is also important to note that 1.25 mg of tibolone daily was used in this trial, while 2.5 mg is usually prescribed for vasomotor symptoms.

11.1.3.3 Phyto-estrogens

These preparations are usually isoflavones, lignans or coumestans, and have been shown to improve menopausal symptoms and may also improve lipid profiles and increase BMD. Despite promising earlier reports,[379] no fracture data are available. These agents cannot, at present, be recommended for the management of osteoporosis.

11.1.3.4 Progestins

As alluded to previously (see 11.1.2.2), the use of progestins alone can neither be recommended for the prevention, nor the treatment, of osteoporosis.

11.1.3.5 Testosterone

The results of genetic (receptor abnormalities) and epidemiologic studies have suggested a role for androgens in the bone health of females.[380] Combined treatment with estrogen and testosterone has been shown to result in significantly higher spine and hip BMD than treatment with estrogen alone.[381,382] Furthermore, conventional HT with estrogen/progestin is associated with a suppression in gonadotropin levels, which may result in decreased ovarian testosterone production; this could decrease osteoblastic bone formation. It has, in fact, been documented that the addition of testosterone prevents the decrease in serum osteocalcin levels (a marker of osteoblast activity) caused by estrogen treatment.[382] Selective androgen receptor modulators (SARMs) bind to the androgen receptor with resulting agonist or antagonist activity, and are presently being tested for muscle wasting and osteoporosis.

In postmenopausal women, testosterone administration has been shown to improve libido and mood. Controlled longitudinal studies on the effects of testosterone on serum lipids and cardiovascular morbidity are, however, necessary before this agent can be recommended for the treatment of osteoporosis in postmenopausal females. The American Endocrine Society warns against the use of testosterone in women, since evidence of safety in long-term studies is lacking.[383]

In hypogonadal males, testosterone (e.g. Depo-Testosterone® 200 mg intramuscular injection every two to three weeks, or three-monthly testosterone undecanoate injections) increases spinal BMD.[12] Bone formation increases, while resorption may decrease. Treatment should be initiated with small doses. Effects on liver function and the lipid profile should be monitored. Testosterone is contraindicated in patients with prostate cancer. In eugonadal men with osteoporosis, six months of fortnightly treatment with 250 mg depot testosterone resulted in a 5% increase in spine BMD, without any change in hip BMD.[384] No fracture data are, however, available in either hypo- or eugonadal osteoporotic subjects treated with testosterone. In general, eugonadal men with osteoporosis are treated with non-hormonal preparations, like the bisphosphonates. Two approaches are followed in the case of hypogonadal men with osteoporosis: some first treat the hypogonadism with testosterone and monitor the BMD response, while others immediately add a bisphosphonate.

11.1.4 Bisphosphonates

The bisphosphonates are synthetic pyrophosphate derivatives that contain a carbon atom instead of an oxygen atom, with the resulting P-C-P bond affording resistance to enzymatic and chemical hydrolysis, and creating a class of drugs which avidly binds to bone and inhibits resorption. Bisphosphonates are forerunners in the treatment of metabolic bone diseases which are characterised by increased bone resorption, like Paget's disease of bone, myeloma and osteoporosis.[385-396]

11.1.4.1 Chemistry, pharmacokinetics and molecular mechanism of action

The P-C-P structure allows for a great number of chemical modifications, either by changing the two lateral chains on the carbon atom, or by esterifying the phosphate groups. This has resulted in the production of a large number of bisphosphonates with varying activity and duration of action. Binding to bone mineral appears to be largely due to the P-C-P structure, while the antiresorptive activity is a function of the side chains and, therefore, the molecule's three dimensional structure.[397,398] The potency of the various bisphosphonates in inhibiting bone resorption differs markedly, as indicated in Table XII.

Table XII: Potency of bisphosphonates in inhibiting bone resorption

~1 x	~10 x	~100 x	100–1,000 x	1,000–10,000 x	> 10,000 x
etidronate	clodronate tiludronate	pamidronate	alendronate	risedronate ibandronate	zoledronate
Non-aminobisphosphonates		Aminobisphosphonates			

Adapted from Fleisch[397]

For the first generation weaker bisphosphonates, like etidronate, the dose required to inhibit resorption is high and close to that which also impairs normal mineralisation, while the more potent aminobisphosphonates do not generally cause osteomalacia. The ability of the bisphosphonates to adsorb to bone mineral also contributes to their potency and, particularly, their duration of action. The binding rank order of bisphosphonates has been shown to be: zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate.[399] This may explain the apparently more prolonged clinical duration of action of zoledronate and alendronate, compared with the more readily reversible effects of risedronate and etidronate.

The intestinal absorption of bisphosphonates is low (< 1%), occurs by passive diffusion and is markedly decreased in the presence of food, calcium, juice and tea or coffee. The drug is cleared quite slowly (early half-life of 10 days) and largely (> 50%) by the skeleton. The rapid intravenous injection of high doses may result in the formation of insoluble aggregates in the circulation, which may impair renal function. The skeletal retention of bisphosphonates is very long (terminal half-life ≥ 10 years) and, under certain circumstances, even life-long.[400] The bisphosphonates localise preferentially at sites of bone resorption where mineral is exposed, are internalised by osteoclasts, are buried in bone during the subsequent cycle of bone formation, and become pharmacologically inactive until they are released at a future time during bone remodelling.[401] Bisphosphonates are not metabolised and are excreted unchanged in the urine. Renal clearance is high.[397]

The mechanism of action of the bisphosphonates on bone is complex and involves a decrease in osteoclast production, an increase in osteoclast apoptosis and a decrease in osteoclast activity.[397-405] Of these, the latter predominates and can be ascribed to the specific inhibition of farnesyl pyrophosphate synthase, an enzyme which regulates the biosynthesis of mevalonate in the cholesterol synthesis pathway.[398,402] This results in the inhibition of protein prenylation and the disruption of key regulatory proteins (e.g. rab, rho, rac) which mediate osteoclast activity.[398,402] The effects of bisphosphonates on osteoblastic bone formation are even more complex. While some have suggested anabolic effects of bisphosphonates on mesenchymal stem cells,[404] the prevailing opinion is that formation is inhibited.[398-402] Whereas some ascribe this merely to the inhibition of resorption and the fact that resorption and formation are generally closely coupled, others have suggested that bisphosphonates cause osteoblast apoptosis and inhibit bone formation directly.[405]

11.1.4.2 Efficacy: effects on BMD, bone turnover and fracture risk

Bisphosphonates prevent bone loss in practically all experimental models of osteoporosis, as well as in normal postmenopausal women, and in men.[385-396] Prevention of bone loss is largely explained by a decrease in bone turnover. The depth of osteoclastic resorption cavities is decreased, fewer trabecular microfractures occur and BMD increases by 2-10%, a feature which is most marked in the first year.

The anti-fracture efficacy of the aminobisphosphonates alendronate (FIT), risedronate (VERT), ibandronate (BONE) and zoledronate (HORIZON) has been extensively documented in more than 30 RCTs.[386,396] The rate of new clinical and morphometric vertebral fractures was generally decreased by 40-60%, but this figure increased to 90% in patients with multiple incident fractures. Absolute risk reduction and number needed to treat (NNT) were usually not stated. Protection against non-vertebral fractures was also documented and, although the rate of hip fractures was decreased by 30-50 %, this was less convincing, generally confined to patients at high risk of fracture, and sometimes required analysis of pooled data from more than one study.

Studies on the anti-fracture efficacy of bisphosphonates have been limited to patients at high fracture risk, i.e. subjects with a BMD in the osteoporosis range (T-score < -2.5) or those with prior fracture. In an RCT, risedronate was shown to be ineffective in protecting against hip fracture in postmenopausal women with osteopenia and a BMD T-score above -2.5.[83] Although a recent post hoc subgroup analysis of pooled data from four different studies claimed that risedronate provided vertebral fracture protection in patients with hip osteopenia,[406] the anti-fracture efficacy, particularly at the hip, of the bisphosphonates in subjects with osteopenia (T-score -1.0 to -2.5) remains questionable. The lack of convincing long-term fracture data in patients treated with bisphosphonates is also noted. In general, fracture data for three to four years are required for regulatory purposes. Although patients

on both risedronate[407] and alendronate[388] have been followed up for seven to 10 years, the utility of these studies, which included very small patient numbers (n < 250) and no suitable placebo group, to monitor sustained fracture efficacy is limited.

Few head-to-head studies comparing the different bisphosphonates have been conducted. Studies have generally compared the magnitude of or the time taken to bring about changes in BMD or biomarkers and, although statistical differences were sometimes found, these were of uncertain clinical importance.[273,408] A recently published cohort study employing more than 40,000 enrollees in large pharmaceutical benefit programmes found no difference in the effectiveness of alendronate and risedronate to prevent non-vertebral fractures.[409] The retrospective cohort VIBE study[410] found that monthly ibandronate was as effective as weekly alendronate or risedronate in reducing hip fractures, and more effective in reducing the risk of vertebral fractures in adherent subjects, results which require prospective validation. To date, no prospective randomised head-to-head studies comparing the *anti-fracture* efficacy of the bisphosphonates have been published. Compliance and adherence are major issue with any chronic medication in relatively asymptomatic patients, and a number of studies have shown that no more than 50% of patients are still taking oral bisphosphonates after one year.[411]

11.1.4.3 Side-effects

Upper gastrointestinal side-effects, including ***nausea***, ***heartburn***, ***chest pain*** and ***vomiting***, are the most common adverse effects encountered in clinical practice, and an important reason for discontinuation of treatment.[408,412-416] Data from RCTs have, however, suggested a much lower incidence (< 1–5%) of these side-effects, which suggests that many patients do not follow the recommendations to take the drug with a ***full glass of tap water*** and ***not recline*** afterwards. Earlier reports suggested that *daily* risedronate was less likely to cause gastrointestinal side-effects than alendronate. Randomised, controlled endoscopic studies also revealed fewer oesophageal erosions and gastric ulcers among daily users of risedronate.[412,413] Recent data from RCTs, like the FACT trial, and systematic reviews have, however, found comparable gastrointestinal side-effects between *weekly* alendronate and risedronate users.[408,414,416] In general, weekly and monthly dosing schedules of bisphosphonates are less likely to cause gastrointestinal side-effects than daily dosing. A recent report of oesophageal carcinoma in patients on alendronate emphasised that this drug should not be prescribed to patients with known erosive oesophageal diseases like Barrett's oesophagus, and recommended that bisphosphonate use should be regarded as a possible risk factor for oesophageal cancer.[415] Subsequent reports have refuted any association between oesophageal cancer and either alendronate or various other bisphosphonates.[417]

Older bisphosphonates, like etidronate, cause ***mineralisation defects***, but the new aminobisphosphonates do not cause osteomalacia.[418] Rapid intravenous injection of a large dose of bisphosphonate may precipitate acute ***renal failure***, a complication which can be avoided by slow infusion.[397] Bisphosphonates are not recommended in patients with a creatinine clearance < 30 ml/minute. Intravenously administered bisphosphonates may induce a transient, although occasionally prolonged, severe ***flu-like syndrome*** characterised by pyrexia, muscle pain, headache and nausea in 15-45% of patients. This is usually a first-dose effect, peaks at 24-48 hours, and disappears within three days. It is thought to represent an acute phase reaction, is accompanied by an increase in C-reactive protein (CRP) (although lymphocyte numbers may either increase or decrease), and can be attenuated by paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDS).[419-421] ***Hypocalcaemia*** may occur when large doses of bisphosphonates are administered intravenously, particularly in children, and can be avoided by reducing the dosage. ***Bone pain*** is sometimes associated with the use of bisphosphonates, but has not been systematically studied and is poorly understood. In an RCT, the intravenous administration of a bisphosphonate has, in fact, been shown to significantly *reduce* pain in patients with recent vertebral compression fractures.[422] A possible association between serious ***atrial fibrillation*** and the use of zoledronate was first reported in the HORIZON study[396] and later extrapolated to alendronate.[423] Two recent meta-analyses, however, refuted any association and, after reviewing data on some 20,000 patients treated with bisphosphonates, the FDA also concluded that no significant relationship between atrial fibrillation and bisphosphonates was apparent.[424,425]

The first report of an association between ***osteonecrosis of the jaw (ONJ)*** and the use of bisphosphonates was published in 2004.[426-431] According to the American Association of Oral and Maxillofacial Surgeons, bisphosphonate-related ONJ (BRONJ) is present if (i) exposed bone is present in the mouth for more than eight weeks (the gingival or mucosal tissue surrounding the necrotic bone is usually, but not always, inflamed and sensitive to touch), (ii) a current or previous history of treatment with a bisphosphonate has been obtained, and (iii) there is no history of prior radiation therapy to the jaw.[427] Early lesions can be demonstrated employing modalities that image bone structure (e.g. panoramic radiographs, CT), bone marrow and soft tissue (e.g. MRI), or functional tests (e.g. ^{99m}Tc-MDP scintigraphy).

A recent review of ONJ noted that, out of 63 cases, more than 80% were patients with an underlying malignancy (usually myeloma or breast cancer), and 90% were receiving intravenous bisphosphonates.[432] In cancer patients administered intravenous bisphosphonates, this relationship appears to be reasonably well established, with a cumulative incidence of 1-12%. Risk factors for the development of BRONJ in these patients include:[426-429]

- Drug-related risk factors (e.g. high dose, potent bisphosphonates and long duration of therapy). It is important to note that the dose of bisphosphonates used to treat cancer

patients is usually *10-fold higher* than those used to treat osteoporosis. A reduction in the dose in oncology practice has already shown that three-monthly administration of intravenous bisphosphonates is significantly safer than monthly administration.[433]

- Dento-alveolar surgery and local oral disease (inflammation, cancer).
- Demographic and systemic factors (advanced age, renal impairment, obesity and diabetes, smoking, alcohol, concomitant chemotherapy).
- Genetic predisposition.

In patients with osteoporosis treated with oral bisphosphonates, the incidence of ONJ is thought to be extremely low, in the order of 0.01–0.0004%.[426-429] In a recent medical claims database study of 260,000 subjects with osteoporosis, the incidence of ONJ in patients receiving bisphosphonates was similar to that of the general population .[434]

The pathogenesis of BRONJ remains poorly defined. Although bisphosphonates are known to inhibit neoangiogenesis and earlier reports hinted at a possible association between ONJ and avascular necrosis of the hip, there is little evidence to support an ischaemic basis for the condition.[428] An association between BRONJ and atypical skeletal fragility resulting from oversuppression of bone turnover (see below) has also been suggested. There is, however, compelling evidence from histologic and radioisotope studies that bone turnover is increased and not reduced within ONJ lesions.[428] Suggestions that the risk of developing BRONJ can be predicted by assessing systemic bone turnover through the measurement of circulating bone turnover marker (BTM) levels, therefore, have no theoretical basis, nor are they supported by any sound experimental evidence. More likely, BRONJ results from bisphosphonate toxicity to bone and/or soft tissue, which is aggravated by infection.[428,431,435,436]

Numerous guidelines have been published on the prevention and management of BRONJ.[426-428] A discussion of these guidelines as they relate to oncology patients falls outside the scope of this guideline. With reference to patients with osteoporosis, it is important to note the following:

- The difference in bisphosphonate doses between oncology and osteoporosis patients must be emphasised. Patients and dentists need to be reassured that BRONJ is extremely rare in the osteoporosis setting. In doses approved for osteoporosis, there does not seem to be a difference in the risk of ONJ, whether bisphosphonates are administered orally or intravenously.[427]
- Good oral hygiene and regular dental visits are recommended. It is, however, not necessary to recommend a dental examination prior to starting bisphosphonate therapy for osteoporosis. If major dental surgery is anticipated, it seems prudent to suggest that this be completed before starting bisphosphonate treatment.
- In those subjects already receiving a bisphosphonate, dental implant placement/surgery is not contraindicated. Some suggest discontinuing the bisphosphonate, but

there are no data to support this practice.[426-428] The use of bone turnover markers has been suggested,[437] but cannot be supported.

- In those subjects with established ONJ, surgical treatment should be conservative, infection should be treated with appropriate antibiotics and pain relief is important, as is referral to an experienced maxillofacial surgeon. Given alternative bone-active agents, it is probably reasonable to discontinue the bisphosphonate.

Atypical fragility fractures (AFFs). In 2000, it was shown that the administration of high doses of the non-aminobisphosphonate etidronate to dogs caused marked suppression of bone turnover, micro-damage accumulation and hypermineralisation.[438,439] This prompted Ott[440] to speculate that chronic alendronate therapy in humans might impair bone strength, given the apparent increase in fracture rate with prolonged therapy. In 2005, Pak et al described nine cases of severely suppressed bone turnover (SSBT) with spontaneous non-spine fractures and delayed fracture healing.[441] Subsequently, no less than eight case reports, four retrospective reviews and one registry-based national cohort study confirmed a higher prevalence of AFF in patients receiving alendronate.[442-446] In March 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK alerted health care professionals about this association, and pointed out that product information for alendronate would be updated to include a warning about atypical stress fractures.[447] In September 2010, the American Society for Bone and Mineral Research (ASBMR) and the FDA published similar reports.

A definitive causal relationship between the bisphosphonates and AFFs remains to be proven and is, in fact, questioned by many. However, although it probably occurs in a very small minority of patients, there is no doubt that we should take cognisance of this condition, which is largely characterised by the following:

- History of chronic (usually longer than five years, but may occur earlier) alendronate use. Limited data are available for the other bisphosphonates in support of a causal association with AFF, but this probably reflects their lower usage and the limited availability of long-term data.
- AFFs most often involve areas rich in cortical bone (e.g subtrochanteric or diaphyseal femur, pelvic bones), and arise either spontaneously or following minimal trauma.
- There is a prodrome of pain and tenderness over the impending fracture site.
- Concomitant use of glucocorticoids or estrogen. May be more common in certain populations (e.g. Asians), and in younger subjects (± 68 years) than those who typically present with an osteoporotic fracture.
- Quantitative bone histology shows suppressed bone turnover, similar to the so-called adynamic bone disease found in a subset of patients with chronic renal failure. Serum biomarkers of bone turnover are usually decreased, but often not as markedly as the bone histology. This is an observation that is compatible with previous reports that

alendronate may exert more marked suppression (> 90%) on bone turnover at the tissue level, compared with only 50% reduction from baseline in biomarker levels.[448,449] Micro-damage (micro-crack quantification) has been shown to be increased in some,[450] but not all,[451] studies.

- X-rays may show typical cortical stress fractures, or a simple transverse or oblique fracture of the femur, with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft.
- Bilateral disease occurs not infrequently. Contralateral pathology often occurs in the same area as the first fracture and may be evident on clinical assessment (e.g. tenderness over the femur shaft), standard radiographs or isotope bone scan.
- History of delayed or absent fracture healing.

Correct management of this syndrome is difficult, given the current state of our knowledge. Clearly, bisphosphonate treatment must be discontinued in the event of an atypical fracture. Contralateral disease should be sought and may require intervention (e.g. prophylactic pinning). Appropriate measures to prevent the development of atypical skeletal fragility include greater awareness of the condition and possibly limiting the duration of bisphosphonate treatment, although no consensus on this issue has been reached (see below).

11.1.4.4 Treatment regimens

Bisphosphonate preparations. Three bisphosphonates are currently registered for the treatment of osteoporosis in this country: daily and weekly oral alendronate with or without vitamin D (branded and generic), risedronate, and zoledronate which is given as an annual intravenous infusion. Given the poor intestinal absorption of the oral bisphosphonates and their potential to cause upper gastrointestinal irritation, these drugs should be taken on an empty stomach with tap water only, and the patient should refrain from reclining after ingestion. It is recommended that calcium and vitamin D intake should be optimised, but these should not be taken simultaneouly with the bisphosphonate.

We have previously expressed concern about the differences in the pharmacological properties of generic alendronate preparations of various manufacturers, as well as the lack of proven clinical efficacy of the generic bisphosphonates.[452,453] Generic bisphosphonates have never been tested for their potency in altering fracture risk or fracture surrogates (BMD, biomarkers). A recent publication by Ringe et al[454] again emphasised the superior safety and efficacy of branded alendronate and risedronate compared with generic alendronate, the use of the latter resulting in a 40–50% lower BMD increase, and two- to threefold more gastrointestinal adverse events.

Duration and monitoring of bisphosphonate therapy. The bisphosphonates have revolutionised the management of osteoporosis over the past two decades. Prolonged

skeletal retention, the emergence of possible long-term complications like ONJ and AFFs, and uncertainty about anti-fracture efficacy beyond four years have, however, required a reassessment as to how long patients should ideally be treated with these drugs, and whether a place for a ***drug holiday*** exists. Furthermore, adherence to long-term oral bisphosphonate therapy is notoriously poor, with 45% of patients being compliant with prescription refills after one year and only 20% continuing treatment after 24 months.[411,455]

Few studies have addressed the issue of a drug holiday. The FLEX trial was an extension of the FIT study, in which 1,099 patients who had been treated with alendronate for five years were then randomised to receive a further five years of alendronate or placebo.[456] Subjects at very high risk (e.g. BMD T-score < -3.5) were excluded. Women who had been switched to placebo lost a statistically significant, but clinically small, amount of bone density, with losses of about 2-3% more than in those who continued taking alendronate for the full 10 years. Biomarker levels likewise increased in the placebo group, but did not exceed pretreatment values. The risk of hip and morphometric vertebral fracture was reported to be similar between those continuing and discontinuing alendronate, although there was a significantly lower risk of *clinical* vertebral fractures in alendronate users. The authors concluded that, for many women, discontinuation of alendronate for up to five years does not appear to significantly increase fracture risk. Results from a post hoc subgroup analysis of FLEX, however, showed that this observation was only true for those women whose BMD at the end of five years was not in the osteoporotic range. The risk of hip fracture was, in fact, increased among individuals in the discontinuation group who had a BMD in the osteoporosis range.[457] Another study assessed the risk of hip fracture after discontinuation of treatment in women compliant with bisphosphonates for two years, and found the risk to be significantly increased; longer duration (three or more years) of bisphosphonate therapy attenuated the increased risk.[457]

It would, therefore, appear that:[456-459]

- Bisphosphonate treatment should continue for four to five years.
- The fracture efficacy of more than four years of treatment with bisphosphonates requires further evidence-based data.
- The implementation of a drug holiday after five years of bisphosphonate treatment is reasonable in those who are not at very high risk of fracture, but must be individualised. In those with high fracture risk, a choice must be made between continuing bisphosphonate treatment and treating with a non-bisphosphonate agent, like strontium ranelate or teriparatide.

11.1.5 Calcitonin

Calcitonin, a peptide hormone produced mainly by the parafollicular cells (C cells) of the thyroid, acts directly on osteoclasts and rapidly decreases bone resorption, largely by

inhibiting osteoclast activity. Calcitonin alters the morphology of osteoclasts and inhibits osteoclastic acid and enzyme secretion.[460] With prolonged administration there is, however, a down-regulation of calcitonin receptors on osteoclasts, and an escape from the suppressive effects of the hormone. When administered in the long term, there is also a reduction in the number of osteoclasts. Since the pharmacological effects of calcitonin on bone are largely attributable to the number of functional osteoclasts present, the magnitude of the skeletal effects of the hormone is proportional to the prevailing rate of bone turnover.[171] Similarly to other ARAs, bone mass increases during the early phases of treatment and then reaches a plateau. Calcitonin also has central, endogenous, opiate-mediated analgesic properties.

11.1.5.1 Efficacy: effects on BMD, bone turnover and fracture risk

Early hypotheses that calcitonin deficiency may cause osteoporosis were disproved and women with osteoporosis have been shown to have similar, if not higher, serum calcitonin levels than do age-matched normal women.[461,462] The bone effects of various calcitonin preparations (e.g. porcine, salmon, eel, human) given as a subcutaneous injection, nasal spray, rectal suppository or pill have, nonetheless, been studied. Some RCTs[463,463] have documented small increases in BMD and a modest suppression of bone turnover, but others failed to show an effect.[465,466] Some small trials, summarised in a meta-analysis,[467] appeared to show a reduction in vertebral fractures following intranasal calcitonin, while an observational study suggested a reduction in the rate of hip fractures following calcitonin treatment.[468]

The largest prospective RCT to determine the efficacy of calcitonin in postmenopausal osteoporosis is the PROOF study,[469] which documented a 36% reduction in the risk of vertebral fractures in subjects receiving 200 IU nasal calcitonin per day. This study was, however, fraught with problems. The trial was only partly blinded, which may be one of the reasons why 59% of participants withdrew from the study and were “lost to follow-up”. No dose response was observed, and only subjects who had received 200 IU/day showed a reduced risk of vertebral fracture. No significant effects were seen with the higher dose (400 IU/day). Finally, no reduction in the risk of hip fracture was evident at any dose.

11.1.5.2 Side-effects

Although calcitonin is safe, up to 30% of patients experience nausea, diarrhoea, flushing and local pain at the site of injection. These occur largely, although not exclusively, with parenteral preparations. Other problems include resistance with long-term usage, and expense.

In summary: Given the limited efficacy of calcitonin in fracture risk reduction, it cannot be regarded as first-line treatment for osteoporosis, and should be reserved for those individuals who are unable to take more effective therapy, e.g. those with impaired renal function.[470] There may be a place for calcitonin in the acute management of painful fracture (e.g. 200 IU nasal calcitonin per day for two to four weeks).[471]

11.1.6 NOFSA recommendations on the use of antiresorptive agents

a. If *adequate amounts of* ***calcium*** (1,200 mg *elemental* calcium per day) and ***vitamin D*** (800-1,000 IU per day) cannot be obtained from the diet, they must be *supplemented.* The yield of elemental calcium in supplements varies with the calcium salt used (Table X). Calcium carbonate should always be taken with meals to ensure adequate absorption. In general, a dose of 500 mg elemental calcium per day is sufficient. Differences between proprietary preparations of calcium supplements are usually not clinically significant. The prophylactic dose of vitamin D may increase to 2,000 IU per day or more during pregnancy and lactation (see 10.3). Cholecalciferol and ergocalciferol are equipotent, and either may be used as supplement. If 25OHD levels suggest vitamin D deficiency, higher doses may be required (e.g. 50,000 IU every two weeks) (GRADE 1/ØØØO).

b. ***Hormone therapy (HT)*** has a useful role in the management of osteoporosis. It should be initiated for specific, proven indications, provided there are no contraindications (Table XI), and treatment should be individualised. For example, consider HT for the treatment of postmenopausal subjects in the 50–60 year age range, with vasomotor symptoms, urogenital atrophy or where deemed appropriate, who are at risk of osteoporotic fracture. The latter may be individuals with DXA-proven osteoporosis (T-score < -2.5), but HT has also been shown to be effective in subjects with osteopenia (GRADE 1/ØØØO).

c. We do not recommend that HT be initiated nor continued *after age 60 years* for the sake of skeletal protection only. Other bone-active drugs are available for this purpose. Continued use of HT in women after age 60 years may, however, be considered if other treatment options are contraindicated (GRADE 1/ØØOO).

d. If *fracture protection* is sought, use doses of HT known to provide fracture protection (i.e. 0.625 mg conjugated equine estrogen, or equivalent). Lower doses of HT have not been confirmed to reduce fracture risk (GRADE 1/ØØØO). Use the therapeutic regimen that is most suitable. For example, in the patient with an intact uterus, estrogen should be opposed by a progestin to provide endometrial protection; consider a transdermal preparation in older individuals and in those with a metabolic syndrome phenotype (obese, glucose intolerant, hypertriglyceridaemia, mild liver disease, smokers) (GRADE 1/ØØØO).

e. Some 10–20% of patients *lose bone mineral density (BMD) despite HT*. Monitoring is, therefore, important. Since a rapid reduction in BMD may

NOFSA recommendations

occur once HT is discontinued, treatment with another bone-active drug at that stage should be considered (GRADE 1/ØØØO).

f. ***Selective estrogen receptor modulators (SERMs),*** *like raloxifene,* cannot be regarded as standard first-line treatment for osteoporosis, but have a role in selected cases. For example, consider these drugs when predominantly vertebral fracture protection is sought in subjects at risk of breast carcinoma. Use with caution in the vasculopath at risk of stroke (GRADE 1/ØØØO).

g. The use of ***tibolone*** for the treatment of osteoporosis is limited by its safety profile, particularly in subjects at risk of stroke (GRADE 1/ØØØO).

h. ***Phyto-estrogens, progestins*** and ***testosterone*** cannot be recommended for the sole purpose of fracture protection in women (GRADE 1/ØØØO).

i. In young, hypogonadal men, ***testosterone replacement*** should be initiated for non-skeletal benefits. We cannot recommend whether a bisphosphonate should be added to the testosterone for skeletal protection right from the start, or whether the skeletal response to testosterone should first be assessed. We suggest that this decision be individualised, based largely on the severity of the bone disease (GRADE 2/ØOOO).

j. ***Bisphosphonates*** should be regarded as first-line treatment for osteoporosis in postmenopausal women, in men and in certain secondary osteoporoses, like glucocorticoid-induced osteoporosis (GIOP) (GRADE 1/ØØØØ).

k. *The anti-fracture efficacy of bisphosphonates* has been limited to patients at high risk, and should therefore largely be reserved for those with a BMD T-score ≤ -2.5 and/or a prior fracture (GRADE 1/ØØOO).

l. Oral bisphosphonates should be taken on an *empty stomach* with *tap water* only, and the patient should *refrain from reclining*. Oral bisphosphonates should not be prescribed to individuals with known upper gastrointestinal disease. Patients administered intravenous bisphosphonates should be alerted to the possible development of a transient, *flu-like syndrome*, and may require treatment with NSAIDs. Bisphosphonates are not recommended in patients with a creatinine clearance < 30 ml/minute. Although first trimester exposure to bisphosphonates does not appear to pose substantial foetal risk, data are very limited and animal and human studies show that bisphosphonates do cross the placenta. The routine use of bisphosphonates *in pregnancy* cannot, therefore, be recommended (GRADE 1/ØØØO).

m. Patients and, particularly, dentists must be reassured that, when bisphosphonates are used in doses approved for osteoporosis (which are usually < 10% of those used in oncology), the *incidence of osteonecrosis of the jaw* is extremely rare and probably no different from that of the general population. A dental examination prior to starting bisphosphonate

therapy for osteoporosis is not indicated. If major dental surgery is, however, anticipated, it seems prudent to suggest that this be completed before initiating bisphosphonate therapy. In those subjects already receiving a bisphosphonate, dental surgery is not contraindicated. We do not recommend stopping the bisphosphonate, nor employing a biomarker of bone turnover to aid in such management (GRADE 1/ØØOO).

n. Following five years of therapy with a bisphosphonate, we suggest that a *drug holiday* be considered in those who are not at high fracture risk, in order to prevent the unlikely development of *atypical fragility fractures (AFFs)*. A recommendation on the duration of such a drug holiday cannot be made, but the patient should clearly be followed up. BMD is usually maintained following the discontinuation of a bisphosphonate, but should be monitored after 18-24 months. In subjects with fractures or a BMD that is still in the osteoporosis range (T-score ≤ -2.5), in those with ongoing risk factors, and in those whose BMD responded poorly whilst on treatment (e.g. did not increase at all or even decreased), treatment with a drug other than a bisphosphonate, like strontium ranelate or teriparatide, should be considered (GRADE 1/ØØOO).

o. No clear difference in the anti-fracture efficacy of the three bisphosphonates registered in this country, *alendronate, risedronate or zoledronate*, is apparent, and no particular bisphosphonate can be recommended. Until further safety and efficacy data become available, we cannot recommend the use of *generic bisphosphonates* (GRADE 1/ØØOO).

p. We cannot recommend the use of ***calcitonin*** as first-line treatment for osteoporosis, and suggest that it be reserved for those individuals who cannot tolerate more effective therapy (e.g. those with a creatinine clearance < 30 ml/minute) (GRADE 2/ØOOO).

11.2 Stimulators of bone formation

Antiresorptive agents (ARAs) reduce, but do not eliminate, fracture risk and do not restore lost bone structure. Anabolic agents have the potential to significantly increase bone mineral density (BMD), restore skeletal microarchitecture and reduce fracture risk to a greater extent than the ARAs. Anabolic agents can increase the number of osteoblast precursors, stimulate the differentiation of these cells into mature osteoblasts, enhance their function, or prolong their survival. Few bone formation-stimulating drugs are, however, available. Although fluoride stimulates bone formation, it does not appear to provide fracture protection. Intermittent low-dose PTH administration is presently the only potent bone formation-stimulating agent available. Improved understanding of osteoblast biology in recent years has, however, paved the way to the development of a number of new agents, which are currently being assessed in clinical trials. These include oral secretagogues of PTH (e.g.

calcilytics or antagonists of the calcium-sensing receptor (CaSR) in the parathyroid glands, which transiently stimulate endogenous PTH secretion); drugs which manipulate osteogenic factors (e.g. BMP or IGF-1 stimulators); and agents which manipulate osteogenic signalling pathways (e.g. modulators of the Wnt signalling pathway, including its natural inhibitors, sclerostin and Dkk-1).[309,472-474]

11.2.1 Parathyroid hormone

11.2.1.1 Mechanism of action

Since primary hyperparathyroidism is characterised by bone pain and fractures, it seems counterintuitive to suggest that the administration of PTH may increase BMD and reduce the risk of fractures. However, like glucocorticoids, the action of PTH on bone differs markedly when intermittent, low-dose administration of the hormone is compared with continuous, high-dose exposure. The former is anabolic, whereas the latter is usually catabolic. Intermittent, low-dose administration of intact PTH or its 1-34 fragment, teriparatide, causes rapid stimulation of bone formation by: (i) directly stimulating the differentiation of preosteoblasts into mature osteoblasts; (ii) stimulating the production of IGF-1, which also facilitates the differentiation of preosteoblasts to osteoblasts but, in addition, prevents osteoblast apoptosis and enhances the differentiated function of the osteoblast to promote bone formation; and (iii) down-regulating the Wnt antagonist sclerostin and thereby augmenting the differentiation of preosteoblasts from mesenchymal stem cells.[473,474] Osteoclastic bone resorption is also increased by PTH but, since this only peaks some 12-24 months later, an "anabolic window" is created which results in a significant increase in areal (dual energy X-ray absorptiometry, DXA) and volumetric (quantitative CT, QCT) bone mass, size and strength, as well as improvements in trabecular microarchitecture (e.g. increase in trabecular number, thickness and connectivity) (Figure 8).

Several studies have demonstrated either no increase or only a small decrease in areal BMD at cortical sites following the administration of intact PTH or teriparatide.[475-478] This has been explained by the fact that PTH increases not only bone mineral content (BMC), but also bone size (BMD = BMC/area), although some increase in endocortical porosity has also been documented. The latter is usually self-limiting and, since periosteal apposition is augmented, cortical thickness is maintained and bone strength is not reduced.

Adapted from Silverman[470] and Canalis et al[474]

Figure 8: The anabolic window

11.2.1.2 Efficacy: effects on BMD, bone turnover and fracture risk

The anabolic effects of PTH in humans were first reported by Reeve et al in 1980.[479] Subsequently, numerous reports have confirmed improvements in BMD, bone remodelling, strength and fracture risk reduction following the administration of PTH/teriparatide. In this guideline, the use of "PTH" without other designation denotes either PTH (1-84) or the hPTH fragment (1-34), teriparatide.

PTH consistently increases areal BMD (aBMD) (measured by DXA) in predominantly trabecular bone, like the spine, by 10–15% over one to three years.[473] The aBMD in mixed cortical/trabecular sites, like the femoral neck, is usually increased by 1-5% over comparable time periods, but aBMD changes over mainly cortical sites, like the distal radius, are inconsistent and may decline.[473,477,480] Volumetric BMD (assessed by QCT) is invariably increased to a greater extent. Treatment with PTH has also been shown to increase spine and hip BMD in men[475,478] and in women with glucocorticoid-induced osteoporosis (GIOP).[476,481,482]

Changes in biomarkers of bone turnover can usually be detected within a month after initiating treatment.[473,483,484] Markers of bone formation increase first, and are followed by an increase in markers of bone resorption (Figure 8).

Following a number of smaller studies on the effects of PTH on fracture risk, the results of a large RCT, the FPT involving 1,637 women with postmenopausal osteoporosis, was published in 2001.[477] Compared with placebo, daily subcutaneous injections of 20 µg hPTH (1-34), for periods as short as 21 months, reduced the risk of new radiographic vertebral fractures by 65%, and non-vertebral fractures by 53%, although separate data for hip fracture prevention are not available. A recent meta-analysis showed that PTH alone or in combination with ARAs reduced vertebral fractures by 64% and non-vertebral fractures by 38%.[35] Using data from the FPT, it was shown that the increase in BMD following teriparatide administration could account for 30–40% of the anti-fracture effect of the drug, the majority of the risk reduction resulting from improvements in non-BMD determinants in bone strength.[485] In a subsequent study, fracture risk reduction was shown to be largely independent of pretreatment bone turnover, although absolute risk reduction was greatest for women with high pretreatment bone turnover.[486] An RCT which compared the efficacy of teriparatide and alendronate in postmenopausal osteoporosis concluded that teriparatide decreased non-vertebral fractures to a greater degree than alendronate.[476] Patient numbers in this study were, however, small (n = 73), the teriparatide dose used was 40 µg/day instead of the recommended 20 µg/day, and some of the fractures included in the analysis may have been traumatic in origin. In an 18-month RCT comparing the efficacy of teriparatide with alendronate in 428 women and men with GIOP, teriparatide was not only shown to increase lumbar BMD significantly more (7.2% vs. 3.4%, p = 0.001), but also decreased vertebral fracture rate more (0.6% vs. 6.1%, p = 0.004), than alendronate. The incidence of non-vertebral fractures was not different.[274] Similar reduced vertebral fracture results have been reported in a 36-month extension of the study (1.7% vs. 7.7%, p = 0.007).[487]

11.2.1.3 Indications for the use of teriparatide

The indications for teriparatide were deliberated by NOFSA and culminated in a position paper which was published in 2004,[488] and recently updated.[489] Taking due cognisance of anti-fracture efficacy, costs, availability of cheaper drugs, adverse effects and the need for daily injections, the following indications for the use of teriparatide are recommended:

(i) Male and female patients over the age of 65 years with a BMD T-score ≤ -2.5; and
- Two or more fragility fractures; or
- Multiple fragility fractures and an uninterpretable DXA, as first-line treatment and alternative to bisphosphonates to avoid possible blunting of the anabolic PTH response when potent ARAs are used initially (see below).

(ii) Patients who have failed treatment with specific bone-active medication, based on:
- Development of new fractures after being on treatment for ≥ 12 months;
- Unacceptable rate of bone loss (e.g. a decrease in vertebral BMD of ≥ 5% per annum), as documented on two or more consecutive follow-up BMD measurements;
- Intolerance to all other bone-active medication.

(iii) Male and female patients on chronic glucocorticoid therapy (three or more months, prednisone equivalent of ≥ 5 mg per day) with:
- BMD T-score ≤ -3.5, without incident fractures; or
- BMD T-score ≤ -2.5 with one or more fragility fracture; or
- Multiple fragility fractures with bone that cannot be assessed by DXA.

11.2.1.4 Side-effects and contraindications

The side-effects of PTH are usually limited to occasional ***nausea***, ***headache*** and ***leg cramps***. A number of metabolic side-effects should, however, be noted. ***Mild hypercalcaemia*** occurs in approximately 10% of patients receiving 20 µg teriparatide daily. Clinically significant ***hypercalciuria*** is reported to be rare (< 1%), does not warrant monitoring in most patients, and is apparently not associated with an increased incidence of renal stone disease.[477,490] Serum ***uric acid levels may increase*** by up to 20%, but clinical gout has not been shown to be more prevalent in patients treated with PTH.

Long-term studies with high-dose PTH, administered to six-week-old Fischer 344 rats, have demonstrated a dose-related increased ***risk of osteogenic sarcoma***.[491,492] This effect is consistent with life-long exposure, in a growing rodent, to high-dose PTH, and is unlikely to have relevance to human bone physiology. Shorter or lower dose exposure to PTH has not resulted in the development of osteosarcomas or other bone tumours. All primate studies have failed to show a similar association and osteogenic sarcomas do not occur with increased frequency in patients with primary hyperparathyroidism, nor were they noted in any of the trials performed in many thousands of patients treated with PTH for up to three years. To date, a single case of osteosarcoma has been reported in more than 300,000 patients treated wordwide with PTH.[493] Table XIII lists the contraindications to the use of PTH/teriparatide that have been suggested by NOFSA.[488]

Table XIII: Contraindications to the use of teriparatide/PTH

Absolute contraindications
• Growing individuals (age < 25 years)
• Pregnancy and lactation
• Pre-existing hypercalcaemia
• Renal impairment (serum creatinine > 180 mmol/l; creatinine clearance < 30 ml/minute)
• Marked increase (≥ 3 x) in liver enzymes
• Neoplasm(s) in the previous five years
• Increased risk of osteosarcoma (e.g. prior skeletal radiation; Paget's disease of bone)
Relative contraindications
• Mild to moderate renal insufficiency (serum creatinine 120-180 mmol/l; creatinine clearance 30–50 ml/minute)
• Moderate increase (≤ 2 x) in liver enzymes
• Possible osteomalacia
• Previous kidney stones
• Gout

11.2.1.5 Treatment regimens

Teriparatide is registered in South Africa for the treatment of osteoporosis, with or without fractures, in postmenopausal women and in men. The intact human recombinant molecule, PTH (1-84), is not available in this country.

Standard treatment. A full assessment (see 9.3), with the emphasis on contraindications (Table XIII), should be undertaken prior to initiating therapy. The recommended dose of teriparatide is 20 µg per day by subcutaneous injection, for a total duration of 18 months.[488,489] A transdermal patch delivery system has been developed and effectively increases BMD, although fracture data are still awaited.[494] Serum calcium and uric acid levels should be monitored at one, six and 12 months of treatment, and the dose of supplemental calcium should be adjusted accordingly.

Combination treatment. As PTH increases both bone formation and resorption, it was initially postulated that combining PTH with an ARA would enhance its effect on bone mass and strength. A number of RCTs have yielded somewhat conflicting data:

- In treatment-naïve subjects, combining PTH with a potent ARA, like alendronate, appeared to blunt the anabolic effects of PTH as adjudged by biomarkers of bone

turnover, as well as areal and volumetric BMD, in both women[495] and men[496] with osteoporosis.

- Concomitant treatment of PTH with less potent ARAs, like estrogen or a selective estrogen receptor modulator (SERM), does not appear to alter the outcome.[497]
- In patients previously treated with ARAs, the anabolic response to PTH depends on the type of ARA, whether a BMD or biomarker response to PTH is assessed, and whether the ARA is switched or added to the PTH. There is general agreement that the best anabolic response to teriparatide, as adjudged by an increase in BMD and improvements in micro- and macroarchitecture, occurs in bisphosphonate-naïve patients. In those previously treated, the anabolic response to PTH depends on the potency of the ARA that was previously used; e.g. previous etidronate users showed a greater increase in BMD than risedronate users who, in turn, showed a greater increase than those who used alendronate.[498,499] The use of three-month on-off cycles of PTH, whilst continuing alendronate treatment, has also been shown to result in a significant increase in BMD, although not as great as that following daily PTH administration.[500] Finally, in women treated with ARAs, greater bone turnover increases were achieved by stopping the ARA and switching to teriparatide, whereas greater BMD increases were achieved by adding teriparatide to the ARA.[497]

These results have been interpreted to imply that (i) the best anabolic response to PTH occurs in bisphosphonate-naïve patients, suggesting a role for PTH as first-line treatment in selected patients with severe disease (see 11.2.1.3); and (ii) in patients currently taking ARAs, adding teriparatide rather than stopping the ARA and switching to teriparatide may confer an improved BMD response. Further studies, employing fracture end-points, are, however, required before this matter is resolved.

Follow-up treatment. Limited data are available on the skeletal response following discontinuation of PTH treatment. While some earlier studies suggested that BMD is maintained, more recent RCTs, including the EUROFORS study, clearly documented a significant decrease in BMD within the first year following discontinuation of PTH. This decline in BMD following discontinuation of PTH appears to be significantly more rapid in women than in men.[501] This rapid bone loss can be prevented by initiating treatment with a bisphosphonate, a SERM or strontium ranelate as soon as the course of PTH has been completed.[501-504]

Retreatment. It remains unclear as to whether a second, discrete retreatment course with teriparatide can produce similar biochemical and BMD changes as seen during the first teriparatide course, since some studies have shown very comparable increases in BMD and in biomarkers of bone formation during retreatment,[505] whereas others have shown a significantly attenuated response with the second course.[506]

11.2.2 Fluoride

Fluoride has fallen into disrepute as treatment for osteoporosis largely due to insufficient anti-fracture efficacy in RCTs. A recent meta-analysis has, however, revealed interesting new data which are briefly reviewed below.

11.2.2.1 Pharmacokinetics and mechanism of action

Sodium fluoride (NaF) is very efficiently (near 100%) absorbed from the gastrointestinal tract. Approximately 50% of the absorbed fluoride is excreted by the kidneys and the remainder is deposited mainly in bone and, to a minimal extent, in other tissues. Skeletal uptake is not homogeneous and proportionately more is taken up by cancellous than by cortical bone. Fluoride affects skeletal tissue (i) by being incorporated into the crystal structure of bone, where it promotes the production of fluorapatite and fluor-hydroxyapatite, which are less soluble than hydroxyapatite and may render bone more resistant to osteoclastic bone resorption; and (ii) as a specific mitogen for osteoblasts, stimulates bone formation at the cellular, tissue and organ level.[507] The molecular mechanism of action of fluoride on osteoblasts remains unclear, although inhibition of phosphatases and augmentation of the mitogen-activated protein kinase (MAPK) signalling pathway, which modulates osteoblast proliferation and differentiation, have been suggested. The response to fluoride treatment is heterogeneous, marked individual sensitivity towards fluoride appears to exist, and approximately one third of subjects do not respond to the administration of fluoride salts at all.[508] Fluoride also decreases the mineralisation of newly formed bone matrix in a dose-dependent fashion. Higher doses of fluoride may cause frank osteomalacia. This may be related, in part, to inadequate calcium/vitamin D intake or absorption.

11.2.2.2 Efficacy: effects on BMD and fracture risk

Earlier observational and randomised controlled studies documented a marked increase in spine BMD and a reduction in vertebral fracture rates following fluoride administration.[509-512] Subsequent RCTs failed to document anti-fracture efficacy and, in fact, suggested an increased risk of non-vertebral fracture.[513-515] A Cochrane review and meta-analysis of 11 RCTs published in 2000 concluded that spine BMD was increased by 8.1% at two years and by 16.1% at four years of fluoride therapy, while the increase in hip BMD was not significant.[516] The risk of new vertebral fractures was unchanged at two and four years, as was the risk of non-vertebral fracture at two years; at four years, the risk of non-vertebral fractures was significantly *increased*. A meta-analysis of 25 RCTs, published in 2008, concluded that there was no significant overall effect on the risk of vertebral or non-vertebral fracture. However, with a daily dose of ≤ 20 mg fluoride equivalents (40 mg NaF/150 mg monofluorophosphate), there was a highly significant *reduction* in vertebral (OR = 0.3, 95% CI: 0.1-0.9) and non-vertebral (OR = 0.5, 95% CI: 0.3-0.8) fracture risk. According to these data, low-dose fluoride treatment provided fracture protection comparable to that of PTH or strontium ranelate.[35]

In summary: A single meta-analysis does not provide the basis for making any rational recommendation regarding the anti-fracture efficacy of fluoride. Moreover, use of this drug is attended by a number of side-effects (e.g gastrointestinal, lower limb pain syndrome), which do not necessarily appear to be dose dependent.[517] Given the very high doses of fluoride employed in previous RCTs (e.g. 75-120 mg NaF per day), the results of future low-dose fluoride studies should, however, be interesting.

11.2.3 NOFSA recommendations on the use of anabolic agents

NOFSA recommendations

a. We recommend that ***teriparatide*** be used in the management of osteoporosis, but only for specific indications. These include subjects with advanced disease (low bone mineral density (BMD) plus fractures), those who have failed antiresorptive therapy and those with severe glucocorticoid-induced osteoporosis (GIOP), as detailed in 11.2.1.3 (GRADE 1/ØØØO).

b. Patients considered for teriparatide therapy should be thoroughly assessed (see 9.3), and contraindications (Table XIII) excluded. The *standard dose of teriparatide* is 20 µg subcutaneous per day, for a *total duration* of 18 months. Serum calcium and uric acid levels should be monitored at one, six and 12 months (GRADE 1/ØØØO).

c. *In patients taking hormone therapy (HT) or a selective estrogen receptor modulator (SERM),* teriparatide should simply be added to the existing treatment (GRADE 1/ØØØO). With *more potent antiresorptive agents (ARAs)*, like the bisphosphonates, it is less clear whether to switch to teriparatide (i.e. discontinue the bisphosphonate) or whether to add the teriparatide. New data do not convincingly show that prior bisphosphonate exposure causes a blunted anabolic response to PTH. Bisphosphonate wash-out prior to PTH therapy is unnecessary and does not influence the treatment effect.[518,519] Current evidence would suggest that the add-on option results in a greater increase in BMD and is probably the preferred choice. Untill fracture data become available, no firm recommendation on combination therapy can, however, be made (GRADE 2/ØOOO).

d. Following *discontinuation of teriparatide treatment*, there is a significant decrease in BMD, particularly in women, and treatment with a bisphosphonate, strontium ranelate or a SERM is indicated to preserve the bone mass gained (GRADE 1/ØØØO).
We cannot make a recommendation regarding the feasibility of *retreatment* once an individual has completed one course of teriparatide. In subjects with severe, fracturing disease, the possibility of another course of teriparatide should, however, not be discounted (GRADE 2/ØOOO).

e. At present, we cannot recommend that ***fluoride*** be used in the treatment of osteoporosis, but have taken cognisance of new data on low-dose therapy and await the results of further RCTs (GRADE 1/ØØØO).

11.3 Drugs with dual or complex actions on bone

11.3.1 Strontium ranelate

The use of strontium in the treatment of osteoporosis dates back over half a century.[520] Recent clinical trials have emphasised the potential of this agent, which is registered for the treatment of osteoporosis in many countries, including South Africa.

11.3.1.1 Pharmacokinetics and mechanism of action

Strontium ranelate is composed of two atoms of the stable non-radioactive trace element strontium, and an organic moiety, ranelic acid. In the gastrointestinal tract, strontium ranelate dissociates into its components: strontium, which influences bone metabolism, and ranelate, which has no pharmacological activity and is eliminated unchanged by the kidneys.[521] The intestinal absorption of strontium ranelate is rather poor (25% bioavailability), and this is reduced by 60-70% if the drug is taken with food or calcium. Strontium ranelate should, therefore, be taken on an empty stomach.

Preclinical studies suggest that strontium ranelate has a *dual mode of action*, resulting in the stimulation of bone formation and the inhibition of resorption. Recent animal studies also suggest that strontium ranelate may promote fracture healing.[522,523] Numerous elegant in vitro studies, largely conducted by Marie and co-workers in France and employing bone cells of rat, mouse, chicken, rabbit or human origin, have demonstrated (i) increased (pre)osteoblast proliferation and differentiation, increased ALP and osteocalcin activity, and enhanced bone collagen synthesis and bone nodule formation following exposure to strontium ranelate; as well as (ii) decreased differentiation, activity and lifespan of cultured osteoclasts.[524-527] The effect of strontium ranelate on osteoblasts is thought to be mediated via the CaSR, since strontium ranelate is known to activate the CaSR which, in turn, activates MAPK and stimulates osteoblast replication.[528] Osteoclast activity may be inhibited by the direct effect of strontium ranelate on these cells, but new data show that strontium ranelate is capable of downregulating the expression of RANKL while enhancing the expression of OPG in osteoblasts, therefore causing marked inhibition of osteoclastogenesis.[529]

Animal studies have generally supported the in vitro data. Biomarkers have documented a decrease in resorption, with an increase in the osteoblast marker, ALP.[530,531] Quantitative bone histology has been less impressive, with some studies demonstrating an increase in bone formation,[524,530-533] while others reported that bone formation was either not increased, was maintained (and not suppressed, as is the case with standard antiresorptive therapy) or only increased following the administration of very high doses of strontium ranelate.[534,535] Clinical trials, including the pivotal SOTI[536] and TROPOS[537] trials, which unequivocally proved the anti-fracture efficacy of strontium ranelate, yielded similar results. The SOTI trial documented a modest 8% increase in bone-specific alkaline phosphatase

(BSALP) and a 12% decrease in the resorption marker CTX. Biomarkers were not reported in the TROPOS study, but bone biopsies from neither of these RCTs revealed significant differences in histomorphometric resorption parameters, nor in the dynamic parameters of bone formation. A modest increase in the mineral apposition rate of subjects receiving strontium ranelate was, however, demonstrated.[538] No evidence of a mineralisation defect was noted in either of these trials. In a recent multicentre, open-label, randomised study comparing the effects of strontium ranelate and teriparatide on bone histology and biomarkers in postmenopausal women with osteoporosis, no biochemical evidence of increased bone formation was documented.[539] Clearly, further studies are required to elucidate the molecular mechanism of action of strontium ranelate in clinical practice.[540]

11.3.1.2 Efficacy: effects on BMD and fracture risk

Following a number of short-term studies, including the phase II PREVOS, the STRATOS and the run-in FIRST trials, results of the phase III SOTI and TROPOS trials were published in 2004 and 2005.[436,537,541]

The three-year SOTI trial of 1,649 postmenopausal women with osteoporosis and at least one vertebral fracture documented that 2 g of oral strontium ranelate daily reduced the risk of new vertebral fractures by 49% and 41% after one and three years of treatment, respectively. After three years, lumbar bone mineral density (BMD) increased by 14.4%.[536] The three-year results of the TROPOS trial of 5,091 postmenopausal osteoporotic women showed a 16% reduction in the risk of non-vertebral fractures. Among women at high fracture risk (age $\geq$ 74 years and femoral neck BMD T-score $\leq$ -2.4), the relative risk reduction for hip fracture was 36%. Strontium ranelate increased the femoral neck and total hip BMD by 8.2% and 9.8%, respectively.[537] These results have been confirmed in a placebo-controlled five-year study,[542] while an open-label extension study showed some evidence for sustained anti-fracture efficacy at eight years.[543]

Although women over the age of 80 years comprise less than 10% of the postmenopausal population, they contribute more than 60% of hip fractures. To determine whether strontium ranelate also reduces fractures in the very old, an analysis based on preplanned pooling of data from the SOTI and TROPOS trials included 1,488 women, aged 80 to 100 years, followed up for at least three years. In an intention-to-treat analysis, the risk of vertebral and non-vertebral fractures were found to be reduced within one year by 59% and 41%, respectively.[544]

Women with osteoporosis (BMD T-score < -2.5) contribute only 26% of hip fractures in the community, whereas most fractures arise from the much larger proportion of women with osteopenia (T-score between -1.0 and -2.5). Although estrogen and selective estrogen receptor modulators (SERMs) have been shown to be effective, bisphosphonates are generally thought to be rather ineffective in preventing fractures, unless BMD is in the osteoporosis range (see

11.1.3.2). Employing data from the SOTI and TROPOS studies, strontium ranelate was shown to reduce the risk of vertebral fractures by 40-50% in patients with osteopenia at the spine and/or the hip.[545] The vertebral anti-fracture efficacy of strontium ranelate has also been shown to be independent of pretreatment bone turnover.[174]

As alluded to above, strontium ranelate administration results in a significant increase in the BMD of the spine and hip. Because strontium is a heavier element (i.e. has a higher atomic number) than calcium, its incorporation into bone will weaken the penetration of X-rays and, therefore, result in an *overestimation of measured BMD*.[546,547] During the first year of strontium ranelate treatment, this effect is maximal and thought to account for approximately 50% of the measured change in BMD. It continues to a lesser degree during the second and third years but, thereafter, the strontium content of bone reaches a plateau, so that any further increase can be entirely ascribed to an increase in bone mass. The use of BMD measurements to monitor the anti-fracture efficacy of ARAs is problematic (see Chapter 12). An excellent correlation between the increase in BMD following strontium ranelate administration and vertebral fracture risk reduction has, however, recently been published; the change in femoral BMD could, in fact, account for 75% of the anti-fracture effect of the drug.[86,548] BMD monitoring during strontium ranelate treatment could, therefore, be valuable to assess both fracture risk reduction and treatment adherence.

11.3.1.3 Side-effects

Strontium ranelate is generally very well tolerated, with ***nausea*** (7%), ***diarrhoea*** (6%), ***headache*** (3%) and ***eczema*** (5%) being the most commonly reported adverse events, but only during the first three months of treatment.[537] Particularly in those with an irritable bowel, it may be advisable to initiate treatment at a lower dose and to gradually increase this over the course of the next two to four weeks.

In pooled data from the SOTI and TROPOS trials, there was an increased ***risk of VTE*** in patients treated with strontium ranelate (0.9% vs. 0.6%). The risk of VTE was small and not progressive between year three and five, strontium ranelate has not been shown to have any effects on haemostasis and, when treatment and placebo arms were corrected for subjects with a prior history of VTE, there was no increase in VTE risk in the strontium ranelate arm.[549] Nonetheless, it is recommended that strontium ranelate be administered with caution in patients at risk of VTE.

During postmarketing surveillance of patients treated with strontium ranelate, cases of ***DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome*** were reported: less than 20 cases for a total of 570,000 patient-years exposure were documented up to 2008.[549] This drug hypersensitivity syndrome is, of course, not unique to strontium ranelate and is caused by a large number of commonly used drugs, including antiepileptics and allopurinol.[550,551] Since systemic involvement (hepatitis, nephritis, endocarditis) can be

fatal, it is important to be aware of the association and to discontinue strontium ranelate if any significant skin disorder occurs within two to three months after initiating treatment.

11.3.2 Vitamin D metabolites

The vitamin D derivatives, calcitriol and alfacalcidol, have been widely studied in postmenopausal women.[552-560] Doses of calcitriol range from 0.25-1.0 μg daily. Alfacalcidol is metabolised to calcitriol via 25-hydroxylation in the liver, and larger doses of this metabolite are generally employed than is the case with calcitriol. These agents stimulate intestinal absorption of calcium, increase serum and urine calcium levels, and decrease PTH and bone resorption. Serum osteocalcin levels increase and there is some experimental evidence that osteoblastic bone formation may be modestly stimulated.[561] Effects on bone mass and fracture rate have been conflicting and may reflect a narrow therapeutic window, as well as coexisting underlying osteomalacia. There is also some evidence of fall protection.[556,559,560]

Three recently published meta-analyses on the effects of vitamin D metabolites on bone reported widely opposing views. A European study[559] suggested that the vitamin D metabolites improved lumbar spine BMD and were more effective than native vitamin D in preventing vertebral fractures, but did not alter the risk of non-vertebral fracture risk significantly. A Canadian meta-analysis of 16 RCTs concluded that the vitamin D metabolites did not reduce the risk of vertebral fractures, but prevented falls and non-vertebral fractures.[560] A Cochrane review stated that there is no evidence of advantage of the analogues of vitamin D over parent vitamin D.[256]

The major potential disadvantage of the potent vitamin D analogues is the relatively common occurrence of hypercalcaemia and hypercalciuria when a calcitriol dose exceeding 0.5 μg daily is used. This may result in kidney stones and renal impairment. Concurrent calcium supplementation should be used with care. Clearly, further studies are required in different populations with different calcium intakes before the full potential of the vitamin D derivatives can be determined.

11.3.3 Anabolic steroids

Anabolic steroids are analogues of testosterone that promote both protein anabolism and masculinisation. The 17-β-esterified derivatives (e.g. nandrolone) are administered parenterally, while the 17-α-methylated steroids (e.g. stanozolol, oxandrolone, danazol) are oral preparations.

Anabolic steroids improve calcium balance, appear to stimulate osteoblast proliferation and inhibit bone resorption.[562-565] Studies have suggested that at least part of the androgenic action on bone may be related to the conversion of androgens to estrogens.[565] Observational and case-controlled studies have suggested a decrease in fracture risk, but the few prospective RCTs published have been unable to convincingly document any

significant anti-fracture effect.[562-564] Anabolic steroids decrease fat mass, increase lean body mass (particularly muscle) and improve muscle strength and coordination.

Stanozolol is usually given continuously at a dose of 5 mg daily. Nandrolone decanoate may be given every four to six weeks at a dose of 50 mg intramuscularly. The use of the anabolic steroids is largely limited by side-effects. The 17-β-esterified derivatives, like nandrolone, cause hirsutism and hoarseness of the voice in a dose-dependent fashion which usually, but not invariably, improves when treatment is withdrawn. The 17-α-methylated steroids, like stanozolol, increase hepatic transaminase levels in about 50% of patients (treatment should be discontinued when levels exceed two times the upper limit of the reference range), and may induce an atherogenic lipid profile. Both classes may increase libido and fluid retention.

Anabolic steroids should be reserved for patients with advanced osteoporosis, particularly the frail and elderly in whom the effects on muscle mass, strength and coordination may be most beneficial. The duration of treatment should not exceed 12 months and potential side-effects should be carefully monitored.

11.3.4 Diuretics

Loop diuretics have been associated with bone loss.[566] Thiazide diuretics, including indapamide, decrease urine calcium wasting, and retrospective analyses of fracture profiles in hypertensive patients have suggested that these drugs may provide fracture protection. No prospective RCT data are available, but a meta-analysis of 13 observational studies, involving some 30,000 subjects, revealed that long-term thiazide use was associated with a 20% reduction in fracture risk.[567]

NOFSA recommendations

11.3.5 NOFSA recommendation on the use of drugs with dual or complex actions on bone

a. ***Strontium ranelate*** should be regarded as *first-line therapy* for postmenopausal osteoporosis. Strontium ranelate has also been shown to provide fracture protection in subjects with osteopenia, including the very old (> 80 years) (GRADE 1/ØØØO).

   Strontium ranelate should be taken on an empty stomach. In those with an irritable bowel, it may be advisable to initiate treatment at a lower dose. Strontium ranelate is best avoided in those with a previous history of VTE (GRADE 1/ØØØO).

   The association, albeit extremely rare, between strontium ranelate and the DRESS syndrome is noted. Strontium ranelate should, therefore, be discontinued if any significant skin rash develops within two to three months of initiating treatment (GRADE 1/ØØØO).

b. The ***vitamin D metabolites***, calcitriol and alfacalcidol, *cannot be recommended* for the treatment of osteoporosis (GRADE 1/ØØOO)

c. ***Anabolic steroids*** have a very small place in the treatment of osteoporosis. In the very old, frail individual with advanced fracturing disease, a short course (e.g. six months) may be considered, largely as an attempt to address the accompanying sarcopenia (GRADE 2/ØOOO).

11.4 The choice of a pharmacological agent

Based on the pathogenesis, clinical features, skeletal sites involved and bone turnover, osteoporosis cannot be regarded as a single disease entity and should be viewed as a *heterogeneous syndrome*. Accordingly, *no ideal drug can be recommended* for the prevention and treatment of osteoporosis. This situation is confounded by the lack of adequate head-to-head comparative studies. A recent systematic review of 76 RCTs and 24 meta-analyses,[414] as well as an assessment of the relative effectiveness of osteoporosis drugs in more than 40,000 enrollees in a pharmaceutical benefit programme,[409] concluded that data are insufficient to determine the relative efficacy or safety of these agents. As with many other chronic degenerative disorders, the choice of pharmacological agent will, therefore, have to be individualised according to (i) the disease profile, (ii) the patient profile, and (iii) available resources and personal preferences.

11.4.1 The disease profile (the osteoporosis syndrome)

The severity of the disease, sites involved (eg. spine vs. hip), causes and risk factors, as well as the rate of bone turnover, may have to be considered before deciding which drug to use.

- If very mild osteopenia without any fractures is present, and no ongoing bone loss seems likely, non-pharmacological measures, coupled with calcium and vitamin D supplementation, and regular follow-up may suffice.
- With more significant osteopenia, hormone therapy (HT) or strontium ranelate should be considered.
- In subjects with DXA-confirmed osteoporosis (T-score ≤ -2.5), a bisphosphonate or strontium ranelate should be considered.
- Bone formation-stimulating agents should be reserved for patients with severe osteoporosis, where mere maintenance of bone mass is not sufficient and a sustained increase in BMD is required.
- The choice of drug is also influenced to some extent by the skeletal site(s) involved. Certain agents, like the selective estrogen receptor modulators (SERMs), have not been shown to protect against non-vertebral fractures and should, therefore, be reserved for reducing the risk of spine fractures.

- Theoretically, high turnover osteoporosis should respond better to antiresorptive agents (ARAs), whereas a low turnover state may indicate the need for bone formation-stimulating agents. This has, in fact, been shown to be the case with some (estrogen, calcitonin),[170,171] but not all (bisphosphonates, strontium ranelate),[172-174] ARAs and further work is required to validate this hypothesis.
- Specific drugs may be indicated if a particular pathogenic process is suspected, e.g. gonadal steroids in hypogonadism, and additional vitamin D if accompanying osteomalacia is suspected.

11.4.2 The patient profile

Age, general health, concomitant disease, patient preference and the clinical setting in which the patient presents may all have a bearing on the initial choice of drug therapy. Accompanying disorders may obviously contraindicate the use of certain drugs or favour the use of others. In younger women (50–60 years), particularly those with menopausal symptoms, HT should be considered, depending on contraindications and patient preferences. If the patient is at risk of breast cancer, a SERM should be considered. When nothing more than a bone-specific drug is required, a bisphosphonate preparation or strontium ranelate may be more suitable. In the frail and elderly osteoporotic patient with marked sarcopenia, a short course of anabolic steroids may also be considered.

In men, young premenopausal women and children, evidence-based data on appropriate osteoporosis treatments are scant. These individuals should, therefore, be referred to specialist centres.

11.4.3 Available resources and personal preferences

Given the lack of comparative data on the efficacy and safety of osteoporosis agents, decisions on drug selection should be individualised and always attempt to accommodate the preferences of the patient. Therapeutic regimens should always be evidence-based and not rationalised on the basis of dwindling resources.

11.4.4 NOFSA recommendations on the choice of a pharmacological agent

a. We acknowledge the fact that, given the heterogeneity of the osteoporosis syndrome and the lack of significant head-to-head comparative studies, ***no ideal drug scenario*** for management can be recommended.

b. ***Drug therapy must be individualised***, taking due cognisance of the disease profile (particularly the severity of bone loss and skeletal sites involved), the patient profile (age, general health, concomitant disease, clinical setting), and the available resources and personal preferences.

12 Monitoring of therapy

As is the case with all chronic degenerative disorders, assessing the response to therapy is an essential part of managing osteoporosis. There is general consensus that clinical assessment and periodic morphometric (radiologic imaging) evaluation are necessary. Controversy, however, surrounds the use of routine bone mineral density (BMD) and biomarker measurements to monitor treatment.

12.1 Clinical assessment

Regular clinical evaluation is important to assess:

- Disease progression: new fractures, progressive kyphosis or loss of height, and pain.
- Drug side-effects.
- Patient adherence to treatment. We have taken note of the fact that less than 50% of patients are still taking osteoporosis drugs after one year, and that this figure falls to around 25% a year later.[411] Reassurance, education and motivation are, therefore, necessary. A clinical assessment three to six months after initiating treatment, followed by an annual check-up, would seem reasonable.

12.2 Vertebral morphometry (imaging)

Vertebral imaging is required when a new compression fracture is suspected, e.g. episodes of acute back pain, progressive loss of height or kyphosis and an unexpected "increase" in lumbar BMD. Since more than half of all new vertebral fractures are asymptomatic, it is also important to obtain lateral radiographs of the spine, or DXA-based vertebral fracture assessment (DXA-VFA), routinely every four to five years to detect new fractures.

12.3 Bone mass measurements

A debate currently rages as to the clinical usefulness of routine BMD measurements following the initiation of osteoporosis treatment. Arguments put forward by those *not in favour* of routine measurements include the following:

- Bone mass measurements employing DXA are too insensitive and reproducibility too poor to detect changes early enough.

- Studies have shown that BMD gains account for only a very small proportion of the reduction in vertebral fracture risk: 28% with risedronate,[568] 16% with alendronate,[569] and 4% with raloxifene,[570] despite a comparable decrease in fracture risk of 30–50%.
- A recent secondary analysis of the FIT study data revealed that 97% of subjects responded to alendronate, with an increase in hip BMD within the first three years after starting treatment, making routine BMD monitoring unnecessary.[571,572]
- In population studies, extreme results of measurements are sometimes partly due to random error, so that, when these measures are repeated, the result is often closer to the mean for the population. This phenomenon is referred to as "regression to the mean". In the FIT and MORE studies, those subjects who displayed increases in hip BMD > 8% during the first year lost an average of 1 % during the second year. In contrast, 83% of those whose hip BMD decreased by > 4% during the first year had increases in hip BMD during the next year, with an overall mean increase of 4.7%.[573]
- Individuals with BMD gain during treatment did not have fracture rates that were lower than those whose BMD remained unchanged during treatment.[574,575]
- No evidence exists that patient adherence to therapy can be improved by BMD measurements. Moreover, poor adherence is a problem in the first three to six months of therapy, not two to three years later.[571,573]

These are all rather compelling arguments. Furthermore, the very theoretical basis for employing a surrogate marker like a BMD measurement to predict the anti-fracture efficacy of a drug, in subjects where the pretreatment baseline rate of bone loss is not known, seems flawed. This concept is best explained in an illustration from a recent publication by Ego Seeman.[576] In Figure 9, in the graph on the left, pretreatment bone loss is high and BMD in the control population decreases by 6% during the three years of therapy. Treatment effectively prevents a 4% loss, but absolute BMD decreases by 2%. In the middle graph, treatment again resulted in a 4% increase in BMD relative to controls, although absolute BMD remained unchanged. In the graph on the right, the same net increase of 4% is the result of a 4% increase in BMD in the treated group, with no change in controls. Treatment was, therefore, successful in all three scenarios but, if the only information available were the BMD in treated patients, the inference would have been that treatment failed in the first two scenarios.

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Figure 9: Pre- and post-therapy changes in BMD[576]

Reprinted from Bone 2007;41:308-317, Seeman E, Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? with permission from Elsevier. Copyright (2007)

It seems quite clear that BMD measurements are anything but ideal surrogate markers to assess the response to therapy. Despite numerous limitations, we do not, however, agree that they are misleading and a waste of healthcare resources, and feel that routine BMD measurements have an important role to play in the monitoring of osteoporosis treatment. Our counterarguments to this effect are listed in the NOFSA recommendations which follow (see 12.5).

12.4 Biomarkers of bone turnover

The bone turnover markers (BTMs) have been discussed in some detail previously (see 7.2.1). Suffice to reiterate here that the use of BTMs potentially allows for early detection/prediction (within three to six months) of a BMD response or anti-fracture effect of treatment that may only become apparent many years later. Theoretically, it is the ultimate tool to assess the response to osteoporosis treatment. For example, during a three-year risedronate trial, changes in urinary CTX and NTX after three and six months accounted for 50–70% of the reduction in vertebral fractures, and 54–74% of the reduction in non-vertebral fractures.[167]

After initiating antiresorptive therapy, markers of resorption usually decline quite rapidly, reaching a plateau after three to six months, whereas bone formation markers usually decrease later and reach a plateau after six to 12 months. The magnitude of the decline depends on the potency and pharmacokinetics of the drug (e.g. treatment regimen, route of administration). Generally, the bisphosphonates and hormone therapy (HT) decrease BTMs by 40–60%, selective estrogen receptor modulators (SERMs) induce a 25–35% decrease, while calcium and vitamin D cause a smaller but significant reduction of about 10–20%.[335,365,577-580] There are also some data to suggest that different antiresorptive agents (ARAs) do not necessarily influence BTMs in the same way. This may reflect different modes of drug action and opens the way to the rational treatment of osteoporosis employing drug combinations. Much more data are, however, required before this can be realised in clinical practice.

The major limitation of using BTMs to monitor osteoporosis treatment involves technical and biological variations when assessing *individual* patients (see 7.2.1.4). This has resulted in most current guidelines not recommending their routine use.[3-7,577]

12.5 NOFSA recommendations on the monitoring of therapy

NOFSA recommendations

a. Regular ***clinical assessment*** is essential to assess disease progression, drug side-effects and adherence to therapy (GRADE 1/ØØØØ). Patient support programmes to improve understanding of the disease and, particularly, adherence to therapy are supported.

b. ***Vertebral imaging***, employing standard radiographs or DXA-based vertebral fracture assessment (DXA-VFA), is indicated whenever a new fracture is suspected (e.g. back pain, loss of height). Since most vertebral fractures are asymptomatic, it is also recommended that vertebral imaging be performed routinely every four to five years (GRADE 1/ØØØO).

c. We recommend that ***routine bone mass measurements*** have a place in the monitoring of osteoporosis treatment (GRADE 1/ØØOO). This recommendation is largely based on the following:

   - Very few biological variables can be measured with the same precision as bone mineral density (BMD). With regular quality control and implementation of the concept of least significant change (LSC) to interpret serial BMD measurements, changes can be appreciated with two-year scan intervals (see 6.1.2.1).
   - Some studies have indeed shown a poor correlation between BMD changes and the risk of vertebral fractures. There are, however, studies which clearly document a significant correlation between vertebral[569,581] and, particularly, non-vertebral[582] fracture risk and BMD changes.
   - The secondary analysis of the FIT study data did reveal an impressive increase in hip BMD in 97% of subjects, which would question the need for routine monitoring. However, other studies had much less impressive results. For example, in the FACT trial, 9% of those treated with alendronate and 14% of those on risedronate showed a significant decrease in BMD.[583] Moreover, we know that, in the real-life situation outside a rigidly controlled drug trial, the response to treatment is even poorer. The very fact that 50% of patients stop taking their medication within one year underscores the principle. In a recent editorial on the subject, Watts et al[584] further point out the dangers of assuming a near-100% response rate to bisphosphonates when generic preparations, known to result in lesser gains in BMD, are used.[454] Studies have also shown that up to 20%

of patients taking hormone therapy (HT) may lose bone, despite apparently adhering to treatment.

- The argument, whether routine BMD measurements are necessary or not, of course has no bearing on the monitoring of patients receiving anabolic agents or strontium ranelate, where up to 75% of the fracture reduction is accounted for by changes in BMD.[86,548]
- Some would argue that the "regression to the mean" principle is a very valid epidemiologic concept, but that it is largely applicable to population studies and not to the management of the individual patient, where a decision on osteoporosis treatment is required.
- Most agree that there is no convincing evidence to suggest that those individuals whose BMD increases on treatment enjoy superior fracture protection compared with those whose BMD remains stable, at least as far as the development of new vertebral fractures is concerned. Greater increases in BMD also do not relate to higher fracture risk reduction. There is, however, evidence that those individuals whose BMD decreased on therapy had higher fracture rates compared with those whose BMD increased or remained unchanged.[574,585,586]
- Poor adherence to treatment, a major problem in the management of patients with osteoporosis, starts early and can only be significantly improved with education and motivation. There are, however, some objective data to suggest that BMD measurement can improve adherence,[87,88] and this is certainly the impression in clinical practice.

In summary: We acknowledge that routine BMD monitoring to assess the response to osteoporosis therapy has limitations, but do not regard these as insurmountable and contend that BMD measurements can be useful, if employed correctly (GRADE 1/ØØOO).

d. ***Only DXA should be used to measure BMD.*** Diligent attention to *quality control* (including in-depth knowledge of the *coefficient of variation (CV) and LSC of DXA machines* used) is crucial. Follow-up BMD measurements should always be made on the same instrument, employing the "compare mode" or "copy mode" function. With few exceptions (e.g. glucocorticoid-induced osteoporosis, GIOP), bone mass measurements *need not be repeated within 18-24 months* after initiating therapy (GRADE 1/ØØOO).

e. ***The first follow-up DXA scan should be interpreted with caution.*** A favourable response (increased or unchanged BMD compared with baseline) should be utilised to motivate and improve patient adherence. A significant decrease in BMD should rarely, if ever, dictate an immediate change in therapy, although a further decrease on subsequent DXA could, and may

still, represent a favourable scenario (see Figure 8), but should alert the care physician to the possibility of poor adherence or an intercurrent disease/bone-toxic drug causing bone loss, despite effective therapy (GRADE 2/ØOOO).

f. ***Bone turnover markers*** should not be used for routine monitoring, but may be employed in problem cases (e.g. to assess suspected poor adherence or treatment failure) (GRADE 1/ØØOO).

13 Treatment of the symptomatic patient

Osteoporosis is not a pain syndrome and uncomplicated disease generally causes few symptoms. Spinal crush fractures are asymptomatic in two-thirds of cases, but may cause severe neuropathic pain, deformity, stiffness, anxiety, insecurity and depression. This results in immobilisation, loss of bone and muscle mass, and predisposition to further fracture. Multiple fractures result in the development of progressive kyphosis, which causes pain, fatigue, dyspnoea, abdominal distention and urinary incontinence. Mobility is further impaired, the head droops, vision is restricted and falls and fractures invariably follow. Effective symptomatic treatment and early rehabilitation following a fracture are, therefore, important.

There is currently no consensus as to the best treatment of the acute painful vertebral fracture, although traditionally this has been rather conservatively managed with analgesia, bed rest, physical support with a brace or corset (short-term only), and subsequent gradual mobilisation. A role for the classical osteoporosis medications has been proposed by some, while others have recommended percutaneous vertebro- or kyphoplasty if pain does not rapidly subside.

13.1 Conventional analgesics

- *Strong analgesics, like opiates* (e.g. morphine and pethidine), should be used for short periods when pain is intense. They decrease anxiety, as well as pain. Opiates, for a few days, and bedrest are often the only measures that provide relief following an acute vertebral fracture.
- *Simple analgesics* can be used as *single* preparations (e.g. paracetamol, aspirin, codeine, propoxyphene and tramadol) or as *combination* preparations (e.g. dextropropoxyphene plus paracetamol, Lentogesic®; tramadol plus paracetamol, Tramacet®).
- *NSAIDs* (eg. indomethacin and diclofenac) may suppress bone formation and fracture healing, and prolonged use should probably be avoided.
- *Tricyclic antidepressants* (e.g. amitryptyline and imipramine) can, in low doses, alter the pain threshold and perception. Much higher doses are required to treat depression.

- *Muscle relaxants* (e.g. baclofen and diazepam). Beware of sedation and subsequent falls.

13.2 Neuromodulation and behavioural modification

Transcutaneous electrical nerve stimulation (TENS), acupuncture and implanted devices employing the "gate theory" of chronic pain control offer acceptable alternatives. Often, simple heat pads and ice packs provide relief. The effectiveness of most treatment regimens will be of limited value unless the cognitive, mood and behavioural aspects of the patient's presentation are also addressed.

13.3 Immobilisation, physiotherapy and hydrotherapy

The acute pain after a limb fracture is usually easy to manage, because fracture pain ceases once the fracture is reduced and immobilised. The pain caused by an acute vertebral fracture requires bed rest, usually for four to 10 days. Although the fracture will take up to 12 weeks to heal, longer periods of immobilisation should be discouraged if further bone loss is to be prevented. Some patients require a brace for one or two months. In the case of dorsal spine fractures, a high brace with shoulder straps and a sternal pad may be prescribed. For lumbar fractures, a Freeman corset usually suffices. Shoes with soft soles should be worn to diminish painful jarring of the spine from the impact of heel strike. In the elderly, a walking frame may provide extra support to help patients mobilise with confidence.

Physiotherapy and hydrotherapy usually entail a structured programme of stretching, strengthening and aerobic exercises to decrease pain, stiffness and deformity. Such physical rehabilitation should, however, only be initiated after the acute fracture phase. Instructions on back care (avoidance of lifting and forward bending) are essential. Chronic pain may affect the lower lumbar and cervical spine as a result of hyperlordosis, which compensates for dorsal kyphosis. This pain is postural and arises from degenerative joint disease and muscle fatigue. Patients must be educated and need to understand this to alleviate anxiety. Appropriate literature is available on the NOFSA website at www.osteoporosis.org.za.

13.4 Osteoporosis medication and pain relief

Classical teaching has it that the specific bone-active drugs improve bone strength and reduce fractures, but do not provide short-term pain relief. Some evidence does, however, exist that intravenous bisphosphonates, teriparatide, strontium ranelate, anabolic steroids and, particularly, calcitonin have direct effects on bone pain.[587]

A central, endorphin-mediated analgesic effect of calcitonin has been recognised for some time. A recent Cochrane meta-analysis of five RCTs concluded that calcitonin (intramuscular

injection, nasal spray or suppository) effectively reduced acute fracture pain within one week, and that this effect continued for at least four weeks.[588-590] It has also been suggested that calcitonin suppresses the excessive bone erosion which develops in the vicinity of a fracture, the so-called "regional accelerated phenomenon of bone turnover". An RCT has documented the prevention of new fractures of the hip in elderly subjects treated with nasal calcitonin.[591] Further studies are, however, required before these preliminary observations can be translated into sound clinical guidelines.

13.5 Vertebroplasty and kyphoplasty

Percutaneous *vertebroplasty* entails the injection, under CT guidance, of a bone cement, like polymethylmethacrylate (PMMA), into a collapsed vertebral body for the relief of pain. *Kyphoplasty* entails the placement and subsequent inflation of a balloon into the trabecular bone of a fractured vertebral body. This compacts the damaged bone and moves it to the periphery, partially restoring the anatomy. Then, PMMA is injected into the void.

Significant pain relief is said to be apparent within 24-48 hours after injection, in up to 80% of patients.[592] The leakage of bone cement into the spinal canal is the most common complication of vertebroplasty and, although it rarely occurs, requires urgent surgical decompression to prevent serious nerve root compression from developing. Very rarely, death due to fat embolism or reaction to PMMA has been reported. Not much long-term data are available but, although no progression of the vertebral deformity treated has been noted, significant increased risk of vertebral fractures in the vicinity of the cemented vertebrae has been suggested by some, although not all, studies.[593,594]

A number of small, non-randomised studies[595-597] and one randomised, open-label trial[598] have suggested that vertebroplasty is superior to conservative treatment in terms of pain management. A systematic review of 11 prospective, three retrospective and one controlled trial in 2006, however, cautioned that there were insufficient data to recommend vertebroplasty.[599] In 2009, the results of two RCTs, the INVEST trial of 131 patients from the Mayo Clinic[600] and an Australian study of 78 participants,[601] were published in the same issue of *The New England Journal of Medicine*. Both studies revealed that vertebroplasty did not differ significantly from the sham-operated control group in terms of measures of back pain, functional disability or quality of life. Criticism on the design of the study and the interpretation of results has largely involved the timing of the procedure, the size of the study groups and the severity of back pain and type of fractures involved.[602] A recent randomised open trial of balloon kyphoplasty in 300 osteoporotic patients (FREE) allowed the authors to conclude that the procedure is both effective and safe.[603] Although the interpretation of the results of the FREE study is compounded by the fact that the study was not blinded (no sham procedure performed), clear differences between the vertebroplasty and balloon kyphoplasty procedures appear to exist, so that results from one study cannot

readily be extrapolated to another. Current evidence would suggest that balloon kyphoplasty should be considered in patients in whom severe back pain persists for six weeks following a recent vertebral fracture.

13.6 NOFSA recommendations on treatment of the symptomatic patient

a. We recommend that the symptomatic acute vertebral fracture syndrome be treated with ***conventional analgesics*** and supplemented with ***heat pads*** and ***ice packs***, as discussed in 13.1 (GRADE 1/ØØØO).

b. The utilisation of ***physiotherapy, hydrotherapy, gradual mobilisation*** and ***back rehabilitation*** is supported (GRADE 1/ØØOO).

c. Given the current state of our knowledge, the use of ***specific bone-active drugs***, like calcitonin, for the treatment of the symptomatic vertebral fracture syndrome does not appear to be cost-effective, and cannot be recommended (USPSTF D/ØOOO).

d. Based on current medical evidence and, in particular, the recently published randomised sham-operation controlled trials, the use of ***vertebroplasty*** cannot be recommended at present. Although firm evidence-based recommendations will have to await further studies, we suggest that ***balloon kyphoplasty*** be considered if severe back pain persists for six weeks following a vertebral fracture, particularly if the loss of vertebral height is no more than 50%, and STIR-MRI (short TI inversion recovery magnetic resonance imaging) reveals the presence of bone oedema, suggesting a recent fracture. Earlier intervention may be considered when the loss of height is more than 50%, whereas the absence of bone oedema on STIR MRI may require that a more conservative wait-and-see approach be considered (GRADE 2/ØØOO).

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APPENDICES

Appendix I

National Osteoporosis Guideline Indaba, Airport Grand Hotel, 30 June 2010

Attendees:

Prof J Pettifor (NOFSA), Dr V Pinkney-Atkinson (UNEDSA), Prof FS Hough (NOFSA), Dr T de Villiers (SAMS, NOFSA), Dr T Kopenhager (SASOG), Dr A Ranchod (RSSA), Prof A Kalla (SARAA), Dr B Tipping (SAGS), Dr D Greeff (JEMDSA, Medpharm Publications), Ms T Hough (NOFSA), Ms B (patient with osteoporosis), Prof M Ngcelwana (SAOA), Ms J van Schoor (PSSA), Ms A Croasdale (National Department of Health), Ms E van der Walt (National Department of Health), Dr L Steyn (SASP), Ms R Rees (ADSA), Dr S Brown (SEMDSA, NOFSA).

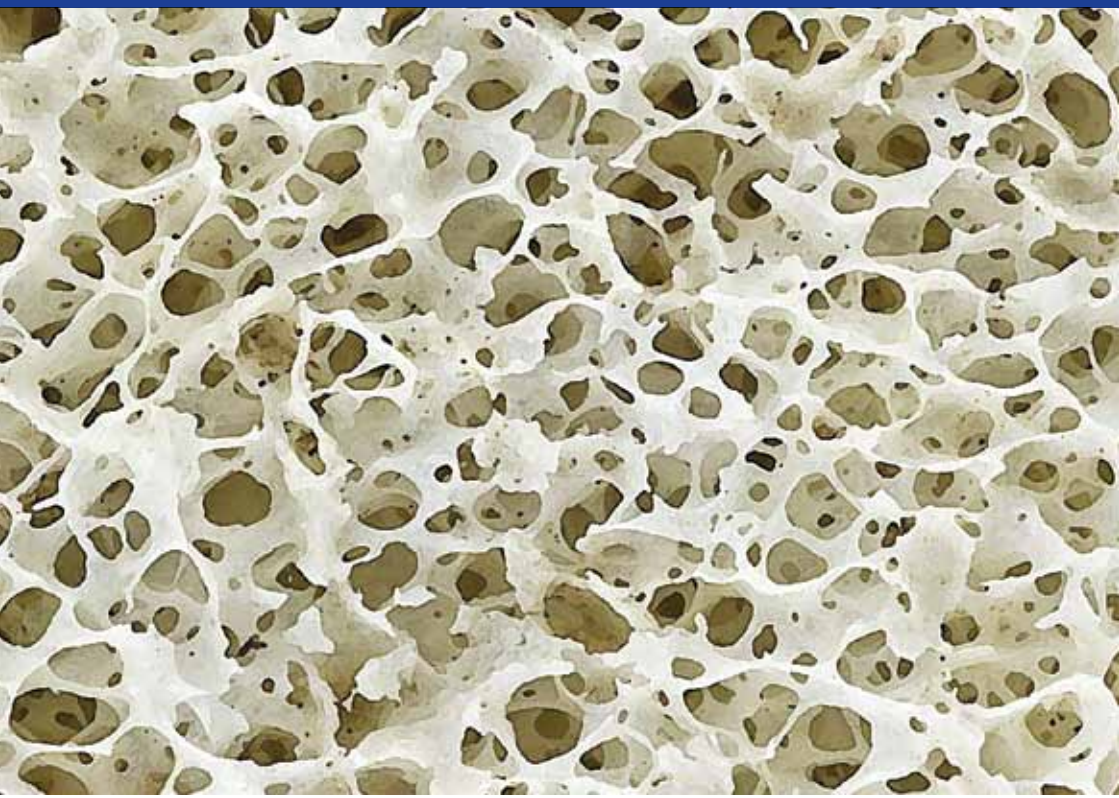
ADSA: Association for Dietetics in South Africa, JEMDSA: Journal of Endocrinology, Metabolism and Diabetes of South Africa, NOFSA: National Osteoporosis Foundation of South Africa, PSSA: Pharmaceutical Society of South Africa, RSSA: Radiological Society of South Africa, SAGS: South African Geriatrics Society, SAMS: South African Menopause Society, SAOA: South African Orthopaedic Association, SARAA: South African Rheumatism and Arthritis Association, SASOG: South African Society of Obstetricians and Gynaecologists, SASP: South African Society of Physiotherapy, SEMDSA: Society for Endocrinology, Metabolism and Diabetes of South Africa, UNEDSA: University-based Nursing Education South Africa

Appendix II

Potential Conflicts of Interest

Listed individuals have served or are currently serving as consultants, advisory board members, speakers, investigators in clinical trials, and/or recipients of unrestricted travel, research or educational grants from the following companies:

Brynne Ascott-Evans	*Eli-Lilly, MSD, Novartis, Sanofi-Aventis, Servier*
Susan Brown	*Eli-Lilly, MSD, Novartis, Novo Nordisk, Servier, Takeda, Wyeth*
Bilkish Cassim	*Eli-Lilly, MSD, Novartis, Sanofi-Aventis, Servier*
Tobie de Villiers	*Adcock Ingram, Bayer Schering, Eli-Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier*
Stephen Hough	*Adcock Ingram, Eli-Lilly, MSD, Novartis, Novo-Nordisk, Sanofi-Aventis, Servier, Takeda, Wyeth*
Stan Lipschitz	*Eli-Lilly, MSD, Novartis, Sanofi-Aventis, Servier.*
John Pettifor	No conflicts of interest
Ernst Sonnendecker	*Arctic Healthcare, Eli Lilly, Schering, Wyeth*



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