NOFSA Guideline for the Diagnosis and Management of Osteoporosis

Executive Summary

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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. This is a detailed summary, which is cross-referenced to the full guideline and is available on the NOFSA (www.osteoporosis.org.za) and JEMDSA (www.jemdsa.co.za) websites.

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 BMD 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 over the age of 50 years of all races. Use BMD 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 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 28) 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.
EXECUTIVE SUMMARY

This is a summary of the detailed guideline available, with references, on the NOFSA (www.osteoporosis.org.za) and JEMDSA (www.jemdsa.co.za) websites. 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 Preamble and guideline 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 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

A draft guideline was compiled by the principal author, debated and revised by the NOFSA council, and finalised at a consensus meeting attended by all relevant stakeholders (Appendix I).

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 (★★★★★), Moderate (★★★★), Low (★★★), and Very Low (★★). 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.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>25OHD</td>
<td>25-hydroxyvitamin D</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatase (total)</td>
</tr>
<tr>
<td>ARA</td>
<td>antiresorptive agent</td>
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<tr>
<td>BMC</td>
<td>bone mineral content</td>
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<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>BMD T-score</td>
<td>BMD value compared to that of the young adult reference mean</td>
</tr>
<tr>
<td>BMD Z-score</td>
<td>BMD value compared to age-, race- and gender-matched controls</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BSALP</td>
<td>bone-specific alkaline phosphatase</td>
</tr>
<tr>
<td>BTM</td>
<td>bone turnover marker</td>
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<tr>
<td>CE</td>
<td>conjugated equine estrogen</td>
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<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>CRF</td>
<td>clinical risk factor</td>
</tr>
<tr>
<td>CTX</td>
<td>C-terminal telopeptides of D-Pyr</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>D-Pyr</td>
<td>deoxypyridinoline</td>
</tr>
<tr>
<td>DRESS</td>
<td>Drug Reaction with Eosinophilia and Systemic Symptoms</td>
</tr>
<tr>
<td>DXA</td>
<td>dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>EPIDEMOS</td>
<td>EPIDemiology of Osteoporosis</td>
</tr>
<tr>
<td>EPISEM</td>
<td>combined EPIDOS and SEMOF cohorts</td>
</tr>
<tr>
<td>EPT</td>
<td>estrogen progesterone therapy</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>ET</td>
<td>estrogen therapy</td>
</tr>
<tr>
<td>FIT</td>
<td>Fracture Intervention Trial</td>
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<tr>
<td>FRAX®</td>
<td>fracture risk assessment tool</td>
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<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
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**EXECUTIVE SUMMARY: Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>GIOP</td>
<td>glucocorticoid-induced osteoporosis</td>
</tr>
<tr>
<td>GR</td>
<td>gradient of risk</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendation, Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HRCT</td>
<td>high resolution computed tomography</td>
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<tr>
<td>HSA</td>
<td>hip structure analysis</td>
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<tr>
<td>HT</td>
<td>hormone therapy</td>
</tr>
<tr>
<td>ICTP</td>
<td>carboxyterminal telopeptides</td>
</tr>
<tr>
<td>IOF</td>
<td>International Osteoporosis Foundation</td>
</tr>
<tr>
<td>ISCD</td>
<td>International Society for Clinical Densitometry</td>
</tr>
<tr>
<td>JEMDSA</td>
<td>Journal of Endocrinology, Metabolism and Diabetes of South Africa</td>
</tr>
<tr>
<td>LH</td>
<td>luteinising hormone</td>
</tr>
<tr>
<td>LSC</td>
<td>least significant change</td>
</tr>
<tr>
<td>NHANES III</td>
<td>Third National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NOF</td>
<td>National Osteoporosis Foundation (USA)</td>
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<td>NOFS A</td>
<td>National Osteoporosis Foundation of South Africa</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NTX</td>
<td>N-terminal telopeptides of D-Pyr</td>
</tr>
<tr>
<td>ONJ</td>
<td>osteonecrosis of the jaw</td>
</tr>
<tr>
<td>OPG</td>
<td>osteoprotegerin</td>
</tr>
<tr>
<td>pDXA</td>
<td>peripheral dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>PICP</td>
<td>C-terminal propeptide of type 1 collagen</td>
</tr>
<tr>
<td>PINP</td>
<td>N-terminal propeptide of type 1 collagen</td>
</tr>
<tr>
<td>pQCT</td>
<td>peripheral quantitative computed tomography</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>PYR</td>
<td>pyridinoline</td>
</tr>
<tr>
<td>QUS</td>
<td>quantitative ultrasound</td>
</tr>
<tr>
<td>QCT</td>
<td>quantitative computed tomography</td>
</tr>
<tr>
<td>RANK</td>
<td>receptor activator of nuclear factor-κβ</td>
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<tr>
<td>RANKL</td>
<td>RANK ligand</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SEMOF</td>
<td>Swiss Evaluation of the Methods of measurement of Osteoporotic Fracture risk</td>
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<tr>
<td>SERM</td>
<td>selective estrogen receptor modulator</td>
</tr>
<tr>
<td>SOTI</td>
<td>Spinal Osteoporosis Therapeutic Intervention</td>
</tr>
<tr>
<td>STIR MRI</td>
<td>Short TI inversion recovery magnetic resonance imaging</td>
</tr>
<tr>
<td>TROPOS</td>
<td>TReatment Of Peripheral Osteoporosis Study</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>VFA</td>
<td>vertebral fracture assessment (see LVA)</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
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 BMD, expressed in relation to the young adult reference mean (the BMD T-score), viz (i) normal, (ii) low bone mass or osteopenia, (iii) osteoporosis and (iv) severe osteoporosis (Table I). 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 guideline (see 6.3, p 61*).

Table I: World Health Organization classification of osteoporosis

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>BMD or BMC (^a) 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)</td>
</tr>
<tr>
<td><strong>Low bone mass</strong></td>
<td>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)</td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td>BMD or BMC value is 2.5 SD or more below the young adult mean</td>
</tr>
<tr>
<td><strong>Severe osteoporosis</strong></td>
<td>BMD or BMC value more than 2.5 SD below the young adult mean, plus one or more fragility fractures</td>
</tr>
</tbody>
</table>

\(^a\) BMC: bone mineral content  
\(^b\) 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.

* Page number refers to the full guideline, available at www.osteoporosis.org.za or www.jemdsa.co.za.
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 BMD measurement 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).
Determinants of skeletal strength and fracture risk

Bone strength is largely determined by bone mass (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). 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) and/or the use of bone-toxic drugs (Table VII) are superimposed on this age-related bone loss, significant osteoporosis may ensue (Figure 2).

Figure 1: Changes in bone mass with age
EXECUTIVE SUMMARY: Determinants of skeletal strength and fracture risk

Bone strength is also influenced by qualitative structural and functional properties which include (i) macroarchitectural factors (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 (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.

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

<table>
<thead>
<tr>
<th>Lifestyle factorsa</th>
<th>Genetic and ethnic factors</th>
<th>Diseases</th>
</tr>
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<tbody>
<tr>
<td>Alcohol (three or more drinks per day)b</td>
<td>Elderly femalesb</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Smokingb</td>
<td>White, Asian and mixed race</td>
<td>Premature menopause</td>
</tr>
<tr>
<td>Low calcium intake</td>
<td>Family history of hip fractureb</td>
<td>Anorexia nervosa/bulimia</td>
</tr>
<tr>
<td>Inadequate physical activity</td>
<td>Osteogenesis imperfecta</td>
<td>Athlete’s amenorrhoea</td>
</tr>
<tr>
<td>Immobilisation</td>
<td>Marfan syndrome</td>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Vitamin D insufficiency</td>
<td>Ehlers-Danlos syndrome</td>
<td>Gastrointestinal disordersc</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Haemochromatosis</td>
<td>Gastric bypass</td>
</tr>
<tr>
<td>Low body mass (BMI &lt; 20)b</td>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Falling</td>
<td>Porphyria</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>High salt/protein intake</td>
<td>Homocystinuria</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>High caffeine intake</td>
<td>Idiopathic hypercalciuria</td>
<td>Gastrectomy</td>
</tr>
<tr>
<td>Excessive exercise</td>
<td>Gaucher’s disease</td>
<td>Pancreatic disease</td>
</tr>
<tr>
<td>Excess vitamin A</td>
<td>Riley-Day syndrome</td>
<td></td>
</tr>
<tr>
<td>Vitamin C, K, B6 and B12 deficiencies</td>
<td>Menkes disease</td>
<td></td>
</tr>
<tr>
<td>Trace element deficiencies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY: Determinants of skeletal strength and fracture risk

### Endocrinopathies\(^d\)
- Cushing’s syndrome
- Diabetes mellitus
- Hyperthyroidism

### Haematologic disorders
- Multiple myeloma
- Systemic mastocytosis
- Thalassaemia

### Rheumatology and immunology
- Rheumatoid arthritis\(^b\)
- Psoriasis

### Miscellaneous
- Alcoholism
- Malignancy
- Fracture after age 40 years\(^b\)
- Parenteral nutrition
- Amyloidosis

### Ageing factors
- Advanced age\(^b\)

### Qualitative factors
- Abnormal bone turnover
- 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.
EXECUTIVE SUMMARY: Determinants of skeletal strength and fracture risk

Figure 2: Pathogenesis of osteoporotic fracture
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 computed tomography (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). There is a limited place for BMD measurement in therapeutic decision making and in patient follow-up (see 6.2.1–6.2.6, pp 57-61*).

* Page numbers refer to the full guideline, available at www.osteoporosis.org.za or www.jemdsa.co.za.
EXECUTIVE SUMMARY: Diagnosis of osteoporosis

1.320
1.200
1.080
0.960
0.840

T = -2.0    Z = -0.6

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

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 1/0000).

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 1/0000).

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 1/0000).
Executive Summary: Diagnosis of Osteoporosis

c. An evidence-based recommendation cannot be made on the most suitable skeletal site at which 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/Ø000).

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) and the NHANES III reference databank. BMD Z-scores should be used in premenopausal women and men under 50 years of age (Figure 3) (GRADE 1/Ø000).

e. The risk of fracture in men over 50 years of age is substantially lower for a BMD measurement 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/Ø000).

f. The diagnosis of osteoporosis in black populations requires local BMD reference values (GRADE 1/Ø000). 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/Ø000).

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/Ø000).

h. BMD measurement 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 is valid (see Table III).

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 1/0000).

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 assessments (DXA-VFA) can be used for this purpose (GRADE 1/0000). The Genant semi-quantitative system (Grade 1–3) should be used to classify fractures (GRADE 1/0000).

**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/m²).
   - 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).
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, for example -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).
- 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 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, 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.
EXECUTIVE SUMMARY: Fracture risk assessment

7.2.1 Bone turnover markers

Bone turnover markers (BTMs) are classified as either markers of bone formation, or markers of bone resorption (Table IV). 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.

Bone turnover markers have been used to (i) identify those at risk of fracture, independent of BMD, (ii) identify those at risk of rapid bone loss, (iii) help rationalise the choice of osteoporosis therapy, and (iv) monitor/predict 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.

Table IV: Biochemical markers of bone turnover

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

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.
EXECUTIVE SUMMARY: Fracture risk assessment

7.3 Ultrasonic bone assessment
There is general agreement that QUS cannot replace central 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 of 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.

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 GR compared with BMD alone (GRADE 1/00000).

b. 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 1/00000). 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 2/0000).

c. Local research on CRFs is urgently required (GRADE 1/00000).

d. 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 1/0000).

e. 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 establish a working group to examine this (GRADE 1/0000).

f. Interpretation of BTM data is made difficult by the lack of any universal definition of what constitutes a “high bone turnover”. Assay-specific reference
EXECUTIVE SUMMARY: Fracture risk assessment

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/ØØ00).

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/ØØ00). Device-specific thresholds should be employed and results should not be applied to the T-score-based WHO diagnostic classification of osteoporosis (GRADE 1/ØØ00).

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/ØØ00). 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/ØØ00).
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 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 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 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 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

For many risk factors, epidemiological studies have employed the relative risk (i.e. the risk of an event in those individuals who have the risk factors, compared with those who do not) over the course of an individual's lifetime. This may be misleading and use of the absolute risk in the short term (e.g. 10 years) is recommended.
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 determine 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.

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. Furthermore, 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 excludes 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.
EXECUTIVE SUMMARY: An integrated approach to fracture risk assessment

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 1/0000). 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 2/0000). 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).

b. *We recommend that treatment should be considered when the DXA T-score is ≤ -2.5 at the hip or spine* (GRADE 1/0000).

c. *We recommend that treatment should 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 CRFs previously identified be utilised in a simple algorithm (Figure 4) to determine the need for treatment (GRADE 2/0000). If the need to intervene is still not apparent, a decision can be made to either use BTMs (intervene if BTM values exceed the upper limit of the premenopausal reference range), or to adopt a conservative wait-and-see attitude and reassess in 18-24 months (GRADE 2/0000). We do not recommend the addition of other risk assessment tools, in particular QUS or QCT, at this stage (GRADE 1/0000).

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 1/0000).
EXECUTIVE SUMMARY: An integrated approach to fracture risk assessment

Clinical risk factors:
- Advanced age
- Prior fracture
- Family history
- Excessive leanness
- Diet/alcohol/smoking
- Fall propensity
- Secondary osteoporoses

Women and men with CRFs

Prior osteoporotic fracture\(^a\)

Measure BMD\(^c\)

T-Score

\(\leq -2.5\)

\(< -1.0\) to \(> -2.5\)

\(\geq -1.0\)

65 - 75 years

\(+\)

\(\geq 2\) CRFs

< 65 years

Yes

No

Individualised assessment of CRFs + BMD

Yes

? (Mode)

No

Consider specific treatment/prophylaxis

Lifestyle changes only

Consider FRAX\(^\text{®}\)

\(^a\) Fracture of wrist, spine, hip, rib, pelvis or humerus.

\(^b\) Also measure BMD.

\(^c\) Hip, spine ± wrist.

Figure 4: Algorithm for the management of osteoporosis in postmenopausal women and men aged 50 years and older.
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 aims of these assessments (Figure 5) are to:

- Confirm the diagnosis of osteoporosis and rule out other metabolic bone diseases (primary hyperparathyroidism, osteomalacia) as the cause of the low bone mineral density (BMD).
- Identify secondary causes of osteoporosis (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, 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.

9.1 Tests to exclude metabolic bone diseases other than osteoporosis

A limited assessment of calcium homeostasis (e.g. serum calcium, albumin, phosphate, parathyroid hormone (PTH), ALP) usually suffices to exclude causes of a low BMD other than osteoporosis, like primary hyperparathyroidism or osteomalacia.

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. 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.

Figure 5: Algorithm for the assessment of patients with osteoporosis
9.3 NOFSA recommendations on the assessment of patients with osteoporosis

a. **Serum calcium, phosphate, albumin, creatinine, total alkaline phosphatase (ALP) and PTH** levels should be assessed in every patient with apparent osteoporosis, to exclude primary hyperparathyroidism and osteomalacia (GRADE 1/ØØØØ). A **serum 25-hydroxyvitamin D (25OHD)** level should be obtained in all elderly patients and, in particular, those who are institutionalised, are housebound or have low sunlight exposure (including the use of sun blockers and 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/ØØØØ).

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 where the menopausal state is uncertain, and urine calcium (GRADE 2/ØOOO).

d. **A number of optional tests**, which should be considered under specific clinical circumstances, are listed in Table V (GRADE 2/ØOOO).
Table V: Recommended laboratory and radiological procedures for osteoporosis

### Routine assessment

- History, physical examination and urinalysis: clinical risk factor and falls assessment.
- Bone mass measurement: spine and hip (distal radius if spine and hip data invalid).
- Vertebral fracture assessment: standard X-rays or 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 when 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, p 60*).
- 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).

* Page number refers to the full guideline, available at www.osteoporosis.org.za or www.jemdsa.co.za.
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

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 listed in Table VI.

**Table VI: Optimal calcium requirements**

<table>
<thead>
<tr>
<th>Group</th>
<th>Daily intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants</strong></td>
<td></td>
</tr>
<tr>
<td>Birth – 1 year</td>
<td>500</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
</tr>
<tr>
<td>1 - 5 years</td>
<td>500</td>
</tr>
<tr>
<td>6 - 10 years</td>
<td>800</td>
</tr>
<tr>
<td><strong>Adolescents/young adults</strong></td>
<td>1,200</td>
</tr>
<tr>
<td><strong>Adult women and men</strong></td>
<td></td>
</tr>
<tr>
<td>25 - 65 years</td>
<td>1,000</td>
</tr>
<tr>
<td>Pregnant and lactating</td>
<td>1,200</td>
</tr>
<tr>
<td>Over 65 years</td>
<td>1,200</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY: Non-pharmacological management of osteoporosis

- Severe prolonged vitamin D deficiency induces osteomalacia, but less marked deficiency causes secondary hyperparathyroidism, increased bone turnover and osteoporosis.
- Protein-energy malnutrition decreases bone formation, and is associated with hypogonadism, muscle weakness and 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). Note that drugs like the anticonvulsants (which promote the catabolism of 25OHD) may cause not only osteoporosis, but also osteomalacia.

10.1.4.1 Glucocorticoid-induced osteoporosis

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. Glucocorticoids may also cause avascular necrosis of the hip.

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 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.

It is often stated that bone loss occurs with a prednisone dose ≥ 7.5 mg per day. Significant bone loss may also accompany therapy with much lower doses, and a marked individual sensitivity to the bone-toxic effects of glucocorticoids is well documented. Traditionally, calcium and vitamin D have been recommended as preventive measures for GIOP, but recently the bisphosphonates have been established as first-line therapy, although the anabolic agents have a role in severe disease.

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

<table>
<thead>
<tr>
<th>Increased risk of osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Excessive thyroid replacement therapy</td>
</tr>
<tr>
<td>Anticonvulsants(^a)</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone, rosiglitazone)</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>Gonadotrophin-releasing hormone analogues</td>
</tr>
<tr>
<td>Chemotherapy(^a)</td>
</tr>
<tr>
<td>Immunosuppressives (cyclosporine, methotrexate)</td>
</tr>
<tr>
<td>Heparin/warfarin</td>
</tr>
<tr>
<td>Chronic lithium therapy</td>
</tr>
<tr>
<td>Prolonged parenteral nutrition</td>
</tr>
<tr>
<td>Aluminium(^a)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased risk of falling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives and hypnotics</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
</tr>
<tr>
<td>Hypoglycaemic agents</td>
</tr>
</tbody>
</table>

\(^a\) May also cause osteomalacia

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) 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. 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.

Table VIII: Risk factors for falling

<table>
<thead>
<tr>
<th>Institutionalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental impairment</td>
</tr>
<tr>
<td>- Dementia, confusion</td>
</tr>
<tr>
<td>- Medication (sedatives, hypnotics, tranquilisers, antihistamines, anticonvulsants)</td>
</tr>
<tr>
<td>- Severe depression (including antidepressants)</td>
</tr>
<tr>
<td>- Alcohol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gait and balance disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Postural hypotension (including antihypertensive drugs)</td>
</tr>
<tr>
<td>- Medication</td>
</tr>
<tr>
<td>- Carotid hypersensitivity</td>
</tr>
<tr>
<td>- Vestibular and proprioceptive disorders</td>
</tr>
<tr>
<td>- Neuropathies, foot disorders</td>
</tr>
<tr>
<td>- Previous stroke</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weakness and immobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Muscle weakness (sarcopenia)</td>
</tr>
<tr>
<td>- Impaired mobility</td>
</tr>
<tr>
<td>- Leaves home less than three times per week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visual impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reduced visual acuity</td>
</tr>
<tr>
<td>- Reduced depth perception</td>
</tr>
<tr>
<td>- Abnormal dark adaptation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental hazards and accidents</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Prior falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>- More than three falls in last year</td>
</tr>
<tr>
<td>- Sideways fall(s)</td>
</tr>
<tr>
<td>- Previous fall(s) with injury</td>
</tr>
</tbody>
</table>
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/ØØØØ).

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/ØØØØ).

c. Monitor serum 25OHD levels in those subjects in whom vitamin D deficiency is likely to be present, viz elderly institutionalised, sun-protected (religious reasons, 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/ØØØØ). 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/ØØØØ).

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/ØØØØ).

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

g. Prevent falls by careful assessment of:
   (i) Medication: Particularly sedatives and hypnotics: attempt to withdraw or 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 exercise programme.
(v) **Cardiovascular status:** Including orthostatic hypotension and carotid sinus hypersensitivity.

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

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

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) to (vii) listed above.

The “get-up-and-go” test measures the time required for a person to rise from a 45 cm-high chair, walk 3 m, turn 180°, return to the chair and sit down. Fifteen seconds to complete the task appears to discriminate best between those at high and low risk of falling.

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

**Glucocorticoid-induced osteoporosis (GIOP)** should be prevented and managed by paying attention 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. Use the lowest effective dose of glucocorticoid, taking due cognisance of marked individual sensitivity and the fact that no dose is safe (GRADE 1/ØØØØØ).
- Alternate-day regimens and high-dose inhaled steroids are also associated with bone loss (GRADE 1/ØØØØØ).
- Obtain a baseline bone mass measurement, sex hormone levels (in men and premenopausal women) and urinary calcium levels. Treat hypogonadism (hormone therapy) and hypercalciuria (indapamide or thiazides) (GRADE 1/ØØØØØ).
- Adequate calcium and vitamin D intake must be ensured, although their value as monotherapy remains uncertain (GRADE 1/ØØØØØ).
- Since only 50% of patients on long-term glucocorticoids will develop GIOP, regardless of the dose, we recommend that a BMD be obtained in all patients. If the 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) are present. If the 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 repeat BMD in six months (GRADE 1/Ø000).

• Bisphosphonates comprise first-line therapy (GRADE 1/Ø000).

• 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/Ø000).

• Remeasure BMD, employing central DXA, within one year of initiating glucocorticoid treatment (GRADE 1/Ø000).
EXECUTIVE SUMMARY: Non-pharmacological management of osteoporosis

Clinical assessment of falls

History of falls in the past year

Recurrent falls

Multifactorial fall management programme

Abnormal gait and balance

Consider:
• Carotid sinus hypersensitivity
• Orthostasis
• Vision

Single fall

Balance and gait assessment ("get-up-and-go" test)

Normal gait and balance

Consider an exercise programme that includes balance and strengthening

No fall

Figure 6: Algorithm for the assessment of falls

a See 10.3 (p 105) of full guideline for details
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). Antiresorptive agents (ARAs) generally maintain bone mineral density (BMD), whereas a sustained increase in BMD is usually accomplished only with use of the anabolic agents (Figure 7).

Table IX: Drugs currently used to treat osteoporosis

<table>
<thead>
<tr>
<th>Inhibitors of bone resorption: anticatabolics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium/vitamin D</td>
</tr>
<tr>
<td>Estrogen/progestins</td>
</tr>
<tr>
<td>Estrogen analogues, selective estrogen receptor modulators (SERMS), testosterone</td>
</tr>
<tr>
<td>- raloxifene</td>
</tr>
<tr>
<td>- tibolone</td>
</tr>
<tr>
<td>- phyto-estrogens</td>
</tr>
<tr>
<td>- testosterone</td>
</tr>
<tr>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>- alendronate</td>
</tr>
<tr>
<td>- risedronate</td>
</tr>
<tr>
<td>- zoledronate</td>
</tr>
<tr>
<td>- pamidronate</td>
</tr>
<tr>
<td>- ibandronate</td>
</tr>
<tr>
<td>Calcitonins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stimulators of bone formation: anabolics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>Fluoride</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs with dual or complex actions on bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strontium ranelate</td>
</tr>
<tr>
<td>Vitamin D metabolites (calcitriol/alfacalcidol)</td>
</tr>
<tr>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Thiazide diuretics/indapamide</td>
</tr>
</tbody>
</table>
Figure 7: Effects on BMD after treatment with ARAs and bone formation-stimulating drugs


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).
Table X: Elemental calcium content of commonly used calcium supplements

<table>
<thead>
<tr>
<th>Calcium salt</th>
<th>Yield of elemental calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>40%</td>
</tr>
<tr>
<td>Tribasic calcium phosphate</td>
<td>38%</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>27%</td>
</tr>
<tr>
<td>Dolomite</td>
<td>22%</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>21%</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>13%</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>9%</td>
</tr>
</tbody>
</table>

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.

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). 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,
EXECUTIVE SUMMARY: Pharmacotherapy of osteoporosis

HT may increase the risk of stroke and coronary heart disease (CHD). Contraindications to the use of HT are listed in Table XI.

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

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

SERMs, for example 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.

See the full guideline (pp 120-123) for details on therapeutic regimens, phyto-estrogens and testosterone.

11.1.4 Bisphosphonates

The bisphosphonates are potent inhibitors of osteoclastic bone resorption. In South Africa, daily and weekly oral alendronate (branded and generic) and risedenrate, as well as zoledronate, which is given as an annual intravenous infusion, are registered for the treatment of osteoporosis (Table XII). Treatment with the aminobisphosphonates results in 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 of vertebral fractures is generally decreased by about 40–50%,
and that of non-vertebral fractures by about 25-35% over 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 after taking the drug. A flu-like syndrome may occur following the intravenous administration of bisphosphonates, but this 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.

Table XII: Potency of bisphosphonates in inhibiting bone resorption

<table>
<thead>
<tr>
<th>-1 x</th>
<th>-10 x</th>
<th>-100 x</th>
<th>100–1,000 x</th>
<th>1,000–10,000 x</th>
<th>&gt; 10,000 x</th>
</tr>
</thead>
<tbody>
<tr>
<td>etidronate</td>
<td>clodronate</td>
<td>tiludronate</td>
<td>pamidronate</td>
<td>alendronate</td>
<td>risedronate ibandronate</td>
</tr>
<tr>
<td>Non-aminobisphosphonates</td>
<td>Aminobisphosphonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Fleisch397

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**

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). 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). 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/ØØØØ).

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 should be *individualised*. For example, consider HT for the treatment of postmenopausal subjects in the 50–60 year age range, with vasomotor symptoms or 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/ØØØØ).

c. We do *not recommend* that HT be initiated nor 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/ØØØØ).

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/ØØØØ). 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/ØØØØ).
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 may have to be considered (GRADE 1/ØØØØ).

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 this drug when predominantly vertebral fracture protection is sought in subjects at risk of breast carcinoma. Use with caution in the vasculopathy at risk of stroke (GRADE 1/ØØØØ).

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/ØØØØ).

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

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/ØØØØ).

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/ØØØØ).

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/ØØØØ). 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/ØØØØ).
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 is extremely rare and probably not different from that in 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/§§§).

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. This may be particularly applicable to cases of GIOP. An evidence-based 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 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/§§§).

o. There is no apparent clear difference in the anti-fracture efficacy of the three bisphosphonates registered in this country, alendronate, risedronate or 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/§§§).

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).

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
EXECUTIVE SUMMARY: Pharmacotherapy of osteoporosis

microarchitecture (Figure 8). 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 glucocorticoid-induced osteoporosis (GIOP).

Figure 8: The anabolic window


Taking cognisance of costs, 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 uninterpretable dual energy X-ray absorptiometry (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).

**Table XIII: Contraindications to the use of teriparatide/PTH**

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Growing individuals (age &lt; 25 years)</td>
</tr>
<tr>
<td>• Pregnancy and lactation</td>
</tr>
<tr>
<td>• Pre-existing hypercalcaemia</td>
</tr>
<tr>
<td>• Renal impairment (serum creatinine &gt; 180 mmol/l; creatinine clearance &lt; 30 ml/minute)</td>
</tr>
<tr>
<td>• Marked increase (≥ 3 x) in liver enzymes</td>
</tr>
<tr>
<td>• Neoplasm(s) in the previous five years</td>
</tr>
<tr>
<td>• Increased risk of osteosarcoma (e.g. prior skeletal radiation; Paget’s disease of bone)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mild to moderate renal insufficiency (serum creatinine 120-180 mmol/l; creatinine clearance 30–50 ml/minute)</td>
</tr>
<tr>
<td>• Moderate increase (≤ 2 x) in liver enzymes</td>
</tr>
<tr>
<td>• Possible osteomalacia</td>
</tr>
<tr>
<td>• Previous kidney stones</td>
</tr>
<tr>
<td>• Gout</td>
</tr>
</tbody>
</table>

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

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) (GRADE 1/0000).

b. Patients should be thoroughly assessed and contraindications (Table XIII) 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 1/0000).

c. In patients taking hormone therapy (HT) or a selective estrogen receptor modulator (SERM), teriparatide may be added to the existing treatment (GRADE 1/0000). 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 2/0000). 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 1/0000).

e. At present, we cannot recommend that fluoride be used in the treatment of osteoporosis (GRADE 1/0000).

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 (pp 147-148) for details.

11.3.5 NOFSA recommendations on the use of drugs with dual or complex action on bone

a. Strontium ranelate should be regarded as 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/ØØØØ).

Strontium ranelate should be taken on an empty stomach. It is best avoided in those with a history of VTE.

Strontium ranelate should be discontinued if any significant skin rash develops within two to three months of initiating treatment (GRADE 1/ØØØØ).

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

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/ØØØØ).
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 the (i) disease profile (the osteoporosis syndrome), (ii) patient profile, and (iii) available resources and personal preferences.

11.4.1 The disease profile (the osteoporosis syndrome)

- If very mild osteopenia without fractures or ongoing bone loss is present, lifestyle changes, with calcium and vitamin D supplementation, 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 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.
Monitoring of therapy

There is consensus that *clinical* assessment and periodic *radiological imaging* are essential. Some controversy surrounds the use of *routine bone mineral density (BMD)* and *biomarker* measurements to monitor treatment.

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, loss of height (GRADE 1/ØØØØ).

c. *Routine BMD monitoring* to assess the response to osteoporosis therapy has limitations, but is clinically useful if employed correctly (GRADE 1/ØØØØ). 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. Furthermore, 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 have higher fracture rates compared with those whose BMD increased or remained unchanged.

d. **Only DXA should be used to measure 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, but should alert the care physician to the possibility of poor adherence or intercurrent disease/bone-toxic drugs (GRADE 2/ØØOO).

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, treatment failure) (GRADE 1/ØØOO).
There is currently no consensus on 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.

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/ØØØØ).

b. The utilisation of physiotherapy, hydrotherapy, gradual mobilisation and back rehabilitation is important (GRADE 1/ØØØØ).

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/ØØØØØ).

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 a 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/ØØØØØ).
REFERENCES

Consult the full guideline on the NOFSA (www.osteoporosis.org.za) or JEMDSA (www.jemdsa.co.za) websites for the complete reference list.
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).


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