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PATHCHAT

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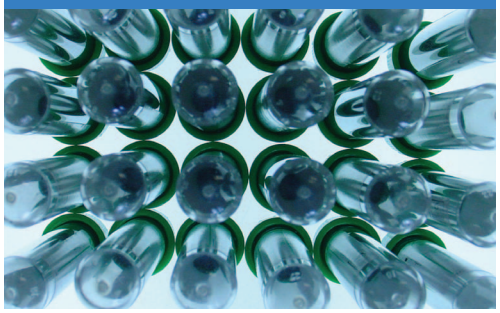


Endorsed by the Ampath Chemical Pathology Peer Group

A practical approach to the biochemical assessment of osteoporosis

The World Health Organisation (WHO) defines osteoporosis (OP) as: "a systemic skeletal disease characterised by reduced bone mass and micro-architectural deterioration of bone tissue that results in decreased bone strength and increased risk of fractures, which usually involves the wrist, hip, vertebrae, pelvis, ribs or humerus".

Recognising the risk of osteoporosis and starting preventative action timeously has become increasingly important. Annually, osteoporosis is responsible for around 9 million fractures worldwide. The lifetime risk of sustaining an osteoporotic fracture above the age of 50 years is up to 40% in women and 20% for men. Osteoporosis is associated with high morbidity and mortality in postmenopausal women and men due to fractures and their complications. About 50% of patients with osteoporotic fractures never regain full functionality. Of those with osteoporotic fractures, 20% die within one year of such a fracture. The high cost involved in the handling of osteoporotic fractures and their complications is another reason for the importance of the early identification of the risk of a fracture. Hospital bed days obtained by osteoporotic fractures exceed those obtained by myocardial infarctions, breast cancer and prostate cancer.

The WHO predicts a threefold rise in the occurrence of osteoporotic fractures over the next 50 years due to an increasing ageing population. Hence, vigilance in assessing those at risk of fracture is of utmost importance.

Overview of osteoporosis

Osteoporosis is a bone disease that is characterised by increased bone turnover with normal bone mineralisation.

In normal bone, continuous remodeling of bone occurs where bone is resorbed by osteoclasts (a process that takes two weeks), and new bone (mostly Type I collagen) is deposited by osteoblasts and then mineralised. The latter two processes take place over a period of six months. In osteoporosis, the birthrate (and not the duration) of these remodeling cycles is increased. This means that resorption exceeds formation, so less bone is available for mineralisation. Bone mass and bone density is decreased, resulting in soft and fragile bone that is vulnerable to fractures.

Osteoporosis can be primary in origin or secondary. Secondary osteoporosis, while not as common, has to be excluded by careful history, examination and special investigations to address underlying causes. A few causes of secondary osteoporosis that are commonly encountered are listed in Table 1.

Table 1: Causes of secondary osteoporosis

Causes of secondary osteoporosis	
Endocrine	Hypogonadism Hyperthyroidism Cushing's Syndrome
Gastrointes-tinal	Partial gastrectomy Malabsorption Chronic liver diseases
Drugs	Glucocorticoids Anticonvulsants Heparin Methotrexate and other chemo-therapies Alcohol Tobacco
Autoimmune diseases	Rheumatoid arthritis Systemic lupus erythematosus
Haematologi-cal	Multiple myeloma Monocytic leukaemia

Diagnosis of osteoporosis

Bone mineral densitometry (BMD) using dual energy X-ray absorptiometry (DEXA) is the current gold standard for the diagnosis of osteoporosis. The WHO criterion for osteoporosis is a BMD or bone mineral content (BMC) that is 2.5 or more standard deviations (SD) below the normal mean for young adults, i.e. normal peak bone mass (or T – score < -2.5).

These assigned thresholds for the diagnosis of osteoporosis (and osteopenia – see section below) are based on total-hip bone mineral density.

The WHO classifies four different categories based on BMD (Table 2). Based on this classification, many patients with osteoporotic fractures are not categorised as patients with osteoporosis (50% of patients with osteoporotic fractures do not have a T-score of less than -2.5) and would therefore not necessarily be placed on anti-resorptive therapy.

Some institutions have changed the value for starting therapy to a T-score of -2, and while this does increase the group of patients qualifying for treatment to a much more significant one, it nevertheless misses a large group of osteoporotic patients, or rather osteopenic patients with significant risk for future osteoporotic fractures.

This problem is partly circumvented by taking into consideration the clinical risk factors associated with increased risk for osteoporosis:

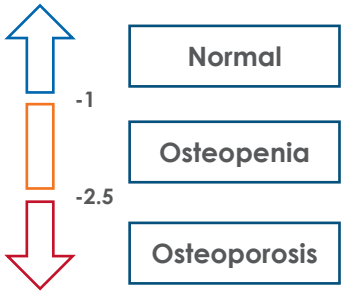
- Age
- Gender
- Race
- BMI
- Inactivity
- Family history of fragility fracture
- Poor nutrition

The use of WHO endorsed or similar software, such as FRAX® (registered software to determine fracture risk) gives a much more comprehensive risk assessment of an individual.

The National Osteoporosis Foundation of South Africa (NOFSA) has acknowledged other shortcomings in the WHO's approach to osteoporosis. These include the following:

Table 2: WHO classification of BMD using DEXA

Category	T-score
Normal	More than -1
Osteopenia	Between -1 and -2.5
Osteoporosis	Less than -2.5
Severe osteoporosis	Less than -2.5 **PLUS** one or more fragility fractures



- Only a single site is used for DEXA T-scoring.
- T-scores cannot be used interchangeably with other imaging techniques that are utilised for BMD determination.
- T-scores are unreliable in population groups other than Caucasian females.
- Bone quality is not taken into account.

The pathogenesis of an osteoporotic fracture is described as being determined by many factors, but it basically constitutes bone quantity (or peak bone mass, determined by age, heredity, exercise, nutrition and normal hormonal function) and bone quality (determined by macro architecture, micro architecture, bone turnover, which also depends on normal hormonal function and proper nutrition, and material properties).

Taking all of this into account, the use of DEXA to determine BMD, in conjunction with clinical risk factors to determine risk for future fractures, can be further refined by the use of biochemical markers.

Biochemical markers used in osteoporosis

Bone turnover markers (Table 3) have as yet not been established in the diagnosis of osteoporosis, even though they can increase the prediction of future fracture risk significantly (especially in the group with a T-score between -1 and -2.5), most notably with the use of the bone resorption markers.

Traditionally, bone resorption markers were measured in urine, while bone formation markers were measured in serum. Many of these markers had well-documented shortcomings, such as non-specificity, instability, poor standardisation of assays or sampling times, considerable pre-analytical variables and the usual challenges associated with urinary samples. Improvement of these assays has left us with reliable, cost-effective, serum-based tests that are being investigated for routine use in screening for osteoporosis.

While NOFSA does not recommend routine use of these tests in screening for osteoporosis, it does, nevertheless, encourage their use in assessing treatment options and monitoring therapy in order to assess suspected poor adherence or treatment failure.

A major advantage of bone turnover markers is that they can be utilised early in follow-up while waiting for DEXA scans to show improvement. A decrease in bone resorption markers of 50% within three months indicates successful therapy, whereas a decrease of bone formation markers of 50% within 6 to 12 months does the same. DEXA changes can only be noted two years after the initiation of therapy.

It is important to note, however, that this must be individualised. Baseline values at diagnosis are therefore imperative in order to follow-up effectively.

The following serum bone turnover markers are available and widely in use:

- *Bone formation markers* – Bone-specific ALP (B-ALP) and osteocalcin
- *Bone resorption marker* – Beta crosslaps (CTX)

Osteopenia

With the population developing osteoporosis being of a more advanced age, the diagnosis of osteoporosis is compounded by the fact that this same age group is vulnerable to osteopenia. Osteopenia (low bone mass) is due to a number of causes, most notably Vitamin D deficiency (osteomalacia) and primary hyperparathyroidism.

Osteopenia is defined as BMD or BMC that is more than 1.0, but less than 2.5 SD below the mean for young adults (T-score between -1.0 and -2.5). Up to 20% of patients with osteoporotic hip fractures have underlying osteomalacia. Osteomalacia has a high prevalence, especially among the elderly, particularly when institutionalised.

Primary hyperparathyroidism has a prevalence of up to 21 in 1 000 women (three times as high as in men).

Treating osteoporosis in the presence of either of these conditions cannot be successful, as mineralisation will never be optimal, despite normalised bone turnover, leaving bones fragile. It is imperative to exclude

these two conditions in screening for osteoporosis and/or prior to initiating treatment.

Table 3: Laboratory markers in the assessment of osteoporosis and osteopenia

MARKERS			
Bone turnover (NOFSA guidelines and currently available marked in **bold**)		**Common causes of OSTEOPENIA**	**Causes of secondary OSTEOPOROSIS**
Bone *formation* markers	**Bone *resorption* markers**		
Bone ALP **Osteocalcin** Procollagen 1 C-terminal peptide (P1CP) Procollagen I N-terminal peptide (P1NP)	Hydroxypro-line Hydroxylysine Pyridinoline Deoxypiridi-noline (DPD) **C-terminal crosslinked telopeptide (CTX or Beta-crosslaps)**	Calcium Phosphate Albumin Parathyroid Hormone 25(OH) Vitamin D	Endocrine: TSH Estadiol, FSH, LH Testosterone Haemato-logical: FBC ESR Serum protein electrophoresis Rheumatoid: Autoimmune markers Others: AST/ALT Creatinine

In conclusion

A practical approach to the use of biochemical markers in the handling of osteoporosis is summarised below

Routine screening for osteoporosis

In conjunction with DEXA and clinical risk factors:

- **Bone turnover markers (especially for osteopenic group)**
  - B-ALP or osteocalcin
  - Beta-crosslaps (CTX)
- **Tests to exclude decreased mineralisation of bone**
  - Vitamin D (25OHD)
  - PTH
  - Calcium
  - Phosphate
  - Albumin
- **Tests to exclude causes of secondary osteoporosis**
  - Full blood count and ESR
  - Creatinine
  - ALP
  - AST/ALT if liver disease suspected
  - Serum protein electrophoresis
  - Estradiol, FSH and LH (females)
  - Total testosterone (men)
  - TSH

Any other tests that are clinically indicated

With diagnosis (at least prior to initiation of therapy)

With baseline DEXA:

- **Bone ALP or Osteocalcin**
- **Beta-crosslaps (CTX)**

With monitoring of treatment

- **Beta-crosslaps (CTX)**
  Bone resorption marker
  Expect a 50% decrease within 3-6 months
- **B-ALP or Osteocalcin**
  Bone formation markers
  Expect a 50% decrease within 6-12 months

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