Malaysian Journal of Medical Sciences, Vol. 8, No. 1, Januari 2001 (11-19)

BRIEF ARTICLE

AN APPROACH TO THE PATIENT WITH OSTEOPOROSIS

Malik Mumtaz

Department of Medicine
School of Medical Sciences, Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan, Malaysia

Osteoporosis is recognised as a public health problem the world over. There is increasing awareness about this problem in Malaysia and this is particularly important, as our population gets older. This brief review aims to highlight the important aspects of history taking as well as the investigative approach to the diagnosis of osteoporosis. The modalities of bone mineral density measurements particularly with regards to the diagnosis and the monitoring of the disease are also discussed.

Key words : *Osteoporosis, diagnosis and monitoring*

Date Accepted 1.1.2001

Introduction

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitecteral deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1). The bone mineral density (BMD) peaks during the third decade of life and declines rapidly around menopause and in the absence of treatment there is an increase in the risk of fractures. It is now a recognised public health problem the world over. There is increasing awareness about this problem in Malaysia and this is particularly important, as our population gets older.

The World Health Organisation (WHO) working group(2) defined osteoporosis in white women on the basis of the bone mineral density criteria shown in table 1. The cutoff value of -2.5 SD below the mean for a young adult (T score) would incorporate 95% of women who eventually sustain a fracture (3). This definition applies only to women.

The approach to a patient with osteoporosis

Table 1 : The World Health Organisation (WHO) working group classification of osteoporosis (2)

Normal	Bone mineral density (BMD) or Bone mineral content (BMC) within 1 SD of young adult reference range
Osteopaenia	Bone mineral density (BMD) or Bone mineral content (BMC) more than 1 SD below the young adult mean but less than 2.5 SD of this value
Osteoporosis	Bone mineral density (BMD) or Bone mineral content (BMC) value of 2.5 SD or more below the young adult mean
Severe Osteoporosis	Bone mineral density (BMD) or Bone mineral content (BMC) value of 2.5 SD or more below the young adult mean and the presence of 1 or more fragility fractures

would involve a through history followed by a complete physical examination. This should be followed by appropriate investigations, which allows the clinician to appropriately manage and follow up the patient.

History Taking and Physical Examination

The history in patients with osteoporosis should begin with the simple question of why the patient presented to your clinic. More often than not, the reason for presentation may be simply concerns about osteoporosis. Osteoporosis has become a household word. Increased awareness can be attributed to advertising campaigns and promotion of healthy life styles and wellness. Other patients may have relatives with osteoporosis.

The most important first step in the diagnosis of osteoporosis is awareness. The silent nature of the disease means those patients often present only after they have sustained a fracture. Some important risk factors for developing osteoporosis include early menopause, a family history of osteoporosis and long-term treatment with corticosteroids. History taking should be through and complete, with a focus on risk factors for osteoporosis, increased susceptibility to falls and the consequences of osteoporosis. Patients may complain of loss of height.

A dietary, menstrual and drug history is equally important. One should also look for features of secondary causes of osteoporosis such as thyrotoxicosis, not forgetting conditions like multiple myeloma. Long-term steroid therapy can lead to significant osteoporosis. One should also inquire about traditional remedies as these may contain steroids.

Physical examination should be meticulous and include height and weight measurements, documentation of kyphosis and deformities and features of secondary causes of osteoporosis.

The history and physical examination will guide the clinician to the diagnosis of osteoporosis. Should patients present with the end result of osteoporosis, the diagnosis is obvious. More often than not patients will the risk factors for osteoporosis but may not have clinically evident fractures and thus would benefit from investigations to quantify bone mineral density outlined below. Clinical criteria are helpful in detecting the at-risk patient. However, they have a weak predictive power and multiple risk factor assessment only predicts 65 % of hip BMD (4).

Table 2 : A suggested scheme of useful investigations in a patient suspected to have osteoporosis

Routine Investigations

Full blood picture and Erythrocyte Sedimentation Rate
Serum Calcium and Phosphate
Renal Function
Liver Function Tests including Albumin
Urine for Bence Jones Protein
Serum Immunoglobulins and protein electrophoresis
Testosterone levels in males
Oestradiol levels in females

X-rays of the spine

Optional Investigations when clinically indicated or if available

Biochemical Markers of Bone turnover
Urinary free Cortisol or 12 midnight/8 am serum Cortisol (suppression tests may be helpful)
Thyroid function tests
Gonadotrophin levels (FSH and LH)
Intact PTH levels

Investigations in Osteoporosis

The main aims of investigation are:

1. To detect osteoporosis
2. To assess present fracture status
3. To determine if there are any underlying treatable or reversible cause of the osteoporosis
4. To provide information which guides the clinician to provide rational, evidence based treatment
5. To monitor the effects of intervention

Preliminary Investigations

A through and complete history and physical examination is followed by basic investigations. The aim of these investigations is to establish a baseline and to screen for secondary causes of osteoporosis. A suggested scheme of investigations is shown in Table 2. Flexibility is important. Further investigations should be based on clinical suspicion. Conventional x-rays of the spine would be a useful to determine the presence of non-clinical fractures and serve as a base line should further x-rays be performed in the future. The lateral spine x-ray of a patient with steroid induced osteoporosis is shown in figure 1.

Biochemical Markers of Bone turnover

The process of continuos bone turnover is termed remodeling. Two processes are involved. They are resorption and bone formation. The bone resorption is controlled by the osteoclasts and the process takes approximately 10 days. This is followed by the laying down of osteoid by the osteoblasts. This process takes 90 days to complete.

Table 3 : Biochemical Markers of Bone Turnover

Resorption Markers
Hydroxyproline
Pyridinoline
Deoxypyridinoline
N-telopeptide of collagen cross-links (NTx)
C-telopeptide of collagen cross-links (CTx)
Formation Markers
Bone specific Alkaline Phophatase
Osteocalcin

The various biochemical markers are shown in Table 3.

Types of Markers

Resorptive markers

During the resorptive process, bone collagen is broken down and the products are excreted via the kidneys. These products can be measured in the urine. The predominant amino acid in collagen is hydroxyproline, which traditionally was used as a marker. It is no longer used to assess bone resorption.

Pyridinoline (PD) and deoxypyridinoline (DPD), products of the breakdown of the pyridinium crosslinks at the collagen triple helix are more specific markers of collagen breakdown. PD and DPD link the telopeptides of one collagen molecule to another. Assays have also been developed for the telopeptides and these are known as NTx and CTx. The later two are also measured in the urine and serum assays should be available before long. Due to diurnal variation in the excretion of these products, the reference period is usually in the morning with the first or second voided sample of urine.

Formation Markers

These appear in sufficient quantity to be measured in the serum. These products include Osteocalcin and bone specific alkaline phosphatase (BSAP). Different assays for Osteocalcin measure different products of breakdown and therefore the same assay or reference laboratory should be used should these tests be repeated.

Clinical Utility of Markers

Biochemical Markers of bone remodeling are not diagnostic tests for osteoporosis. They are useful in the monitoring the response to therapy. Although optional and not practical in this country, response to therapy can be measured 3-6 months of therapy with biochemical markers of bone turnover well before changes are seen on BMD measurements. An adequate response to therapy will cause a > 30% reduction in the markers as compared to pre-treatment levels (5). There is a plateau effect seen as long as treatment is sustained (2). The acute response of biochemical bone markers is predictive of the subsequent response of the bone mass over 2 years and thus measurements at baseline and at 3 months is likely to be helpful in management of

osteoporosis.

Bone turnover marker assays are not widely performed in Malaysia and are mostly limited to research institutions. The biggest limiting factor is the cost of such tests.

Bone Mineral Density (BMD) measurements and the Risk of Fractures

With the advent of BMD measurements, the quantification of risk has been an important advancement in osteoporosis. The bone mass is an important determinant of fracture risk. Prospective studies from as far back as the 1970s and the 1980s with earlier BMD measurement techniques of photon emission absorptiometry confirm the ability of such measurements to evaluate the risk of fracture. The study of osteoporotic fractures (SOF) has confirmed that hip bone density is the best predictor of hip fractures and that hip BMD is as good a spinal BMD for fractures (7). There is a two to three fold increase in the risk of fracture for each standard deviation reduction in BMD (8).

Indications for BMD measurements

Bone mineral density measurements should be performed on all patients who are at risk of osteoporosis. Suggested indications for measurement are shown in Table 4. The decision to test for BMD should be based on an individual's risk profile and **testing is never indicated unless the results could influence a treatment decision**

Quantification of Bone mineral Density

Current Techniques for BMD measurements include

I. Axial BMD measurements (Spine and Hip) performed with Dual energy X-ray absorptiometry (DXA)

II. Peripheral BMD measurements

Various Techniques for the measurement of BMD at peripheral sites fall under this category. These include:

A. Single Photon emission absorptiometry (SPA)
B. Single energy X-ray absorptiometry (SXA)
C. Peripheral DXA (pDXA)
D. Quantitative Ultrasonography (QUS)

Table 4 : Clinical risk factors providing indications for the diagnostic use of bone densitometry

Presence of strong risk factors
Oestrogen deficiency
- Premature menopause (<45 years of age)
- Prolonged secondary ammenorrhoea
- Primary hypogonadism

Corticosteroid Therapy (>7.5 mg daily for 1 year or more)
Maternal family history of hip fracture
Low Body Mass Index (less than 19 kg/m^2)
Other conditions associated with osteoporosis
- Anorexia Nervosa
- Malabsorbtion
- Primary hyperthyroidism
- Chronic Renal Failure
- Hyperthyroidism
- Prolonged immobilisation
- Cushing's Syndrome

2. Radiological osteopaenia and or vertebral deformity
3. Previous fragility fractures of hip, spine and wrist
6. Loss of height, thoracic kyphosis

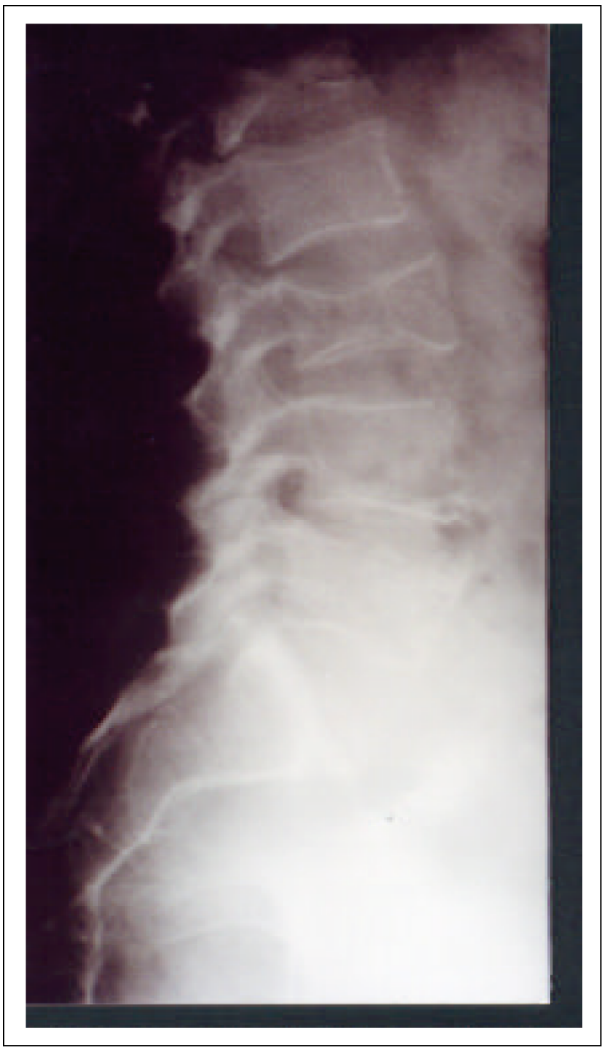
(from Kanis JA et al Guidelines for the diagnosis and Management of Osteoporosis. Osteoporos Int.1997; 7:390-406.) (7)

I. Axial Skeleton BMD measurements

Dual energy X-ray absorptiometry (DXA)

The fundamental physical principle behind DXA is the measurement of the transmission of x-rays with high and low photon energies through the various tissues in the body (10, 11). The radiation burden is small (2.6-34 μSv depending on the type of machine used) (12). The technique is simple and easy to perform. The WHO criteria for the diagnosis of osteoporosis referred to in Table 1 are based on DXA values. DXA therefore is the non-invasive gold standard for the diagnosis of osteoporosis

Figure 1 *A lateral lumbar-sacral spine x-ray of a patient with steroid induced osteoporosis. There is significant radiological osteopaenia with decrease in the height of the vertebrae and end plate sclerosis. Note the presence of the fishbone appearance of the L3 vertebra. These appearances are typical of osteoporosis*



In most patients bone mass is best measured at the anterior-posterior (AP) lumber spine and the hip. This gives the best assessment of the risk of axial fractures and the diagnosis of osteoporosis at these sites (3). Osteoporosis is a systemic disease and thus measurement at any site should be able to provide some information regarding the skeletal status (5). However because of the lack of total correlation between sites, osteoporosis at one site is not invariably associated with changes at the other site and therefore assessment of the appropriate site is preferred. Risk assessment is therefore best assessed by BMD measurement at the site of concern.

One must be aware of the pitfalls of the AP lumbar spine values as factors such as compression fractures and osteoarthritic changes can confound the results. Newer DXA machines can perform lateral scans and this may improve the ability to detect BMD changes in the osteoarthritic spine.

Interpretation of DXA Results

One must be familiar with the manufacturer's result plot. There are different types of DXA machines available on the market each with different accuracy, precision, different diagnostic algorithms and different reference ranges. The normal ranges are not local and machines available in Malaysia use reference values from other Asian countries. Malaysian values for the main ethnic races should be available in the near future.

Results for a DXA scan expresses the mass of bone mineral per unit projected area (g/cm^2) averaged over the region of interest (ROI), which may be L2-4, L1-4 for the spine and the total hip. Interpretation of results can be confusing. A DXA scan performed on one manufacturer's machine cannot be directly compared with another, as the raw BMD result will be different(13). Computer software is now available for the standardisation of spine BMD measurements (14). Femoral BMD values are more difficult to standardize. A normal LunarCorp DXA densitometer plot for the hip and lumbar spine is shown in figures 1 and 2.

The T score is the parameter that is now widely used for the interpretation of the result. It measures the departure of the subject's BMD from the mean BMD of a young group of normal adults aged 20-35 matched for age, sex and race.

$$\text{T score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young Adult SD}}$$

The Z score is the parameter that is similar in concept to the T-Score. It measures the departure of the subject's BMD from the mean BMD of a group of normal adults matched for age instead of a young adult population. This value would be useful in older patients.

$$\text{Z score} = \frac{\text{Measured BMD} - \text{Age Matched mean BMD}}{\text{Age Matched SD}}$$

II. Peripheral bone mineral density measurement techniques

Osteoporosis is a systemic disease and thus affects the entire skeleton. Peripheral measurements of BMD can predict the risk of fractures at the hip and spine(15). Studies on modalities such as SPA and QUS have demonstrated the ability to assess fracture risk (21).

Single X-ray absorptiometry (SXA) and Peripheral DXA (pDXA)

The use of SPA is outdated and largely succeeded by SXA and pDXA for measurements of the peripheral skeleton. X-rays have replaced the use of photons for the bone density measurement. SXA technology requires a water-bath while pDXA does not.

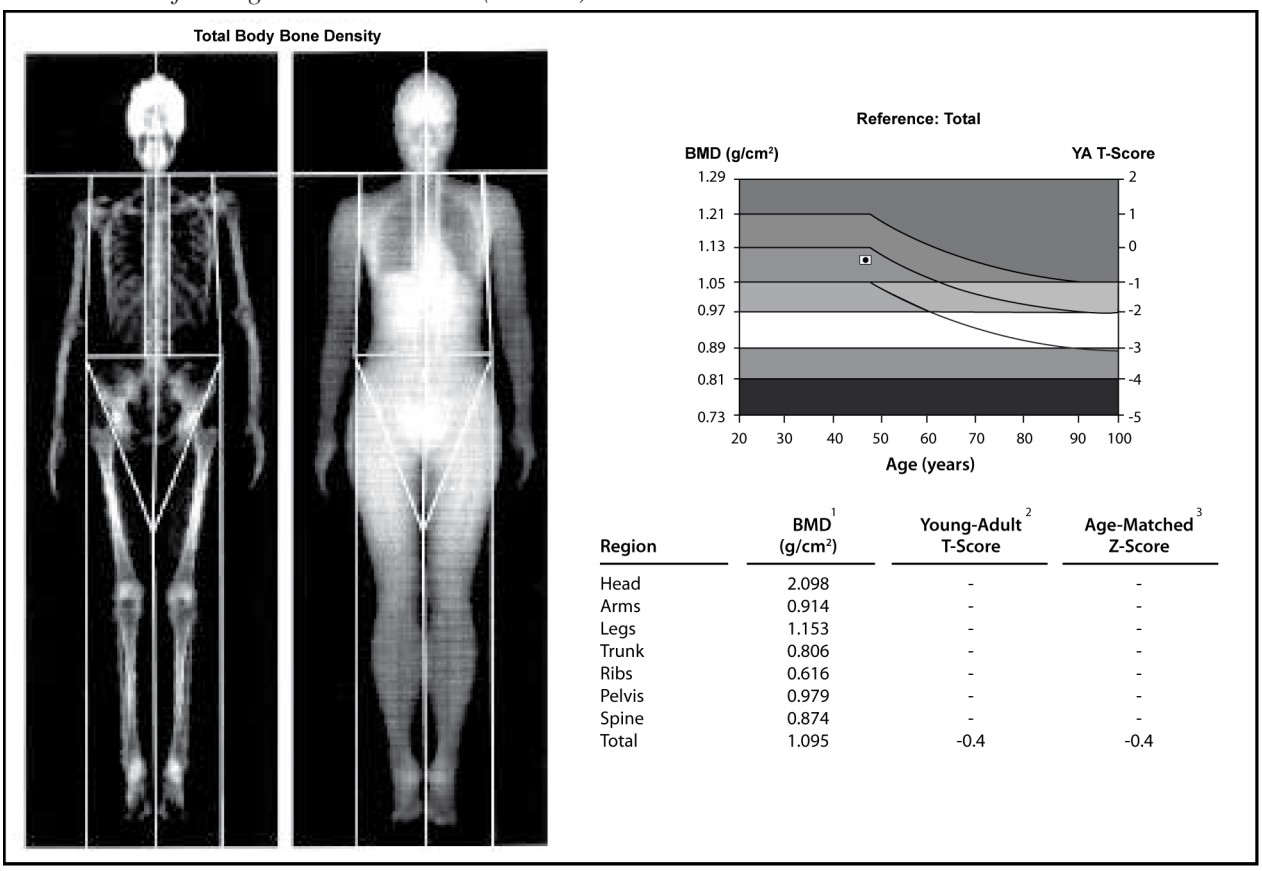
SXA devices have been shown to predict all non-spine fractures about as well as DXA The first prospective studies to evaluate the association between bone density and Fractures were published in the 1970s. Almost all measures derived from SPA and SXA as well as DXA have been shown to predict fracture risk with little differences in their ability to predict future fracture risk (21).

Peripheral DXA devices offer the advantages as SXA with the added advantage of a simpler positioning procedure. There are only a few studies addressing the issue of the performance of pDXA and it remains to be seen how its performance compares with its predecessor (15).

Quantitative Ultrasound

In recent years, there has been interest in finding an alternative method of assessment of

Figure 2 *A normal DXA result for BMD measurement of the hip. The patient's BMD value is plotted on the graph and can quickly allow the user to determine the status of this patients BMD with that of the age matched control (T score)*



Region	BMD[1] (g/cm²)	Young-Adult[2] T-Score	Age-Matched[3] Z-Score
Head	2.098	-	-
Arms	0.914	-	-
Legs	1.153	-	-
Trunk	0.806	-	-
Ribs	0.616	-	-
Pelvis	0.979	-	-
Spine	0.874	-	-
Total	1.095	-0.4	-0.4

skeletal status. Quantitative ultrasound (QUS) measurement of the heel is perhaps the most promising technique. Bone ultrasound devices use frequencies in the range of 0.2-1.0 MHz and measure two parameters namely broadband ultrasonic attenuation (BUA) and the speed of sound (SOS) (11).

One must be aware that there are many systems on the market, each having its own method of measurement and normal range. The advantage of the ultrasound devices is that they are portable and could potentially be used in more rural areas, there is no exposure to ionising radiation and the machines are relatively cheap. Experience has suggested that ultrasound may provide information about architecture (19). Studies have demonstrated an increase in the risk of fractures with decreasing QUS results(17, 18) and this data can be used to predict fracture risk in older women. QUS parameters have also demonstrated changes in the immediate postmenopausal period (20).

There are drawbacks of this technique. The diagnosis of osteoporosis is a challenge for QUS. It remains to be seen how the definition of osteoporosis developed for BMD by DEXA can be translated into an ultrasound diagnosis.Ultimately it may be possible to diagnose osteoporosis on QUS alone. At this time there is no consensus on how results of QUS devices should be interpreted in order to diagnose osteoporosis (21). There is also very little experience in monitoring the changes over time solely by QUS. Problems with this modality include the diversity of techniques, the lack of standardisation and comparable normal ranges. QUS measurements correlate well with BMD measurements in the heel but correlation with other sites is only modest. There is no doubt QUS will have an important role to play in the management of osteoporosis once the issues discussed above are sorted out. This technique offers patients with limited access to densitometry the opportunity to have some form of measurement. Patients with an enhanced risk of fractures should have additional measurements by DXA. At this time one should not rely on QUS alone. DXA would help to define the exact extent of the problem and would be crucial in monitoring the response to therapy.

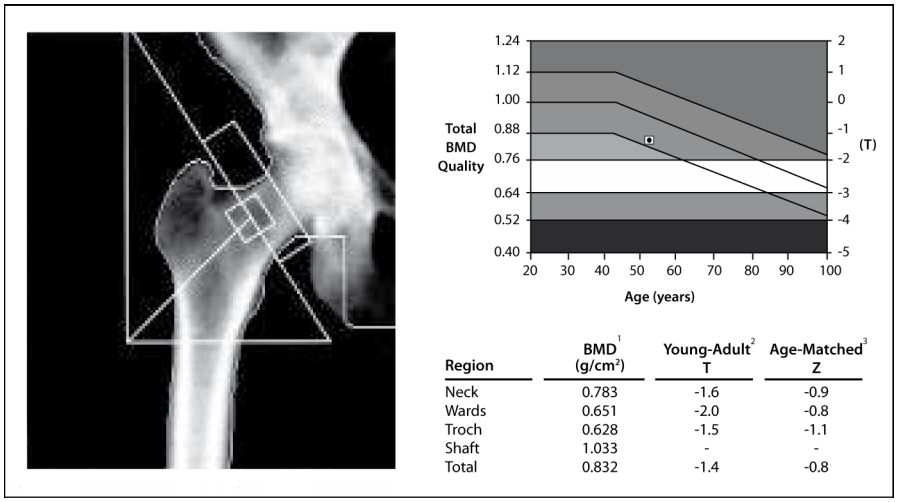
Monitoring of Therapy

A host of agents are now available for the treatment of osteoporosis. In the era of evidence-based medicine some of these agents such as Alendronate, an amino-bisphosphonate, are backed with large multi-centre trials proving the efficacy of these agents. It is therefor important to monitor the effects of treatment and document the reduction in fracture risk.

The aim of follow-up should be to:

1. evaluate response to therapy and reinforce need for therapy
2. assess compliance to medication, life style modification and exercise
3. deal with any problems that patients may have with therapy
4. answer any questions that patients may have and allay fears

Figure 3 A normal DXA plot of the spine BMD measurement.



Patients should be seen 3-6 months after initiating therapy and thereafter annually if possible (22).

General measures

Every follow up visit should include careful history taking on loss of height, new fractures, recent onset back pain, compliance to therapy and any problems with treatment. Physical assessment of weight and height is mandatory. In case of loss of height of 1 cm or more and back pain, lateral x-rays of the spine are indicated (9).

Response to Therapy

The main aim of therapy in osteoporosis is to prevent further bone loss and decrease the risk of fractures. Although optional and not practical in this country, response to therapy can be measured 3-6 months of therapy with biochemical markers of bone turnover. These changes occur well before a response is seen on BMD measurements. An adequate response to therapy will cause a > 30% reduction in the markers as compared to pre-treatment levels (6). There is a plateau effect seen as long as treatment is sustained (9). The acute response of biochemical bone markers is predictive of the subsequent response of the bone mass over 2 years and thus measurements at baseline and at 3-6 months is likely to be helpful in management of osteoporosis.

Gain in bone density is more modest. An important consideration is the precision of the technique. Precision is the degree to which repeated measurements vary and depends on a number of factors including the equipment used for measurement and the anatomical site of measurement (22). The long-term precision in the most precise methods, i.e. SXA and DXA is in the order of 1-2%. A change of 3-6% in BMD is therefore required before one can demonstrate the effectiveness of therapy(9).

One should not repeat BMD measurements until completion of 1-2 years of therapy and every two years there after. In patients with secondary osteoporosis such as corticosteroid-induced osteoporosis, more rapid bone loss can be expected and more frequent BMD measurements may be helpful (3). Assessment of response to therapy should be at axial sites, particularly at the spine due to its metabolically active trabecular bone.

Small changes in BMD are seen at peripheral sites and the precision of measurements make monitoring at these sites unreliable(1). Due to limited experience with ultrasonography of the heel, the monitoring of skeletal changes solely by means of QUS cannot at this time be recommended (21).

Conclusion

In conclusion, the diagnosis of osteoporosis in those who are asymptomatic begins with a high index of suspicion. Through history taking and physical examination is followed by simple investigations. BMD measurements should ideally be performed by DXA although peripheral measurement techniques may be used to stratify those patients who are at high risk of fractures and these individual can subsequently be referred for DXA studies. Bone turnover markers are useful for the monitoring of therapy but cannot be used to diagnose osteoporosis.

Correspondence :

Dr. Malik Mumtaz MD (USM) MRCP (UK),
Department of Medicine,
School of Medical Sciences,
Universiti Sains Malaysia,
16150 Kubang Kerian, Kelantan, Malaysia.
Telephone Number +609 765 1711
e-mail Mumtaz@kb.usm.my

References

1. Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med* 1993; **94**: 646-50
2. WHO technical report series 843. *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis*. Geneva: World Health Organisation, 1994
3. Ryan PJ . Overview of the role of BMD measurements in managing osteoporosis.*Semin Nucl Med* 1997;**27**: 197-209
4. Slemenda CW, Hui SL, Longcope C, Wellman H, Johnston CCJR. Predictor of bone mass in perimenopcwsal women. A prospective study of clinical data using photon absorptiometry. *Ann Intern Med* 1990; 112: 96-101.
5. Kleerekoper M. Using bone remodeling markers in osteoporosis treatment. *Patient care*. 1999; **28**: 121-130
6. Meunier PJ, Delmas DD, Eastell R, McLung MR Papaoulos S, Rizzolir, Seeman E, Washich RD. Diagnosis and Management of Osteoporosis in Postmenopausal Women: Clinical Guidelines.*Clinical Therapeutics*. 1999; **21**: 1025-1044

7. Cummings SR, Black DM, Nevitt MC, Browner, Cauley J, Ensrudk, Genant HK, Palermol L, Scott J, Vogt TM: Bone Density at various sites for prediction of hip fractures. *Lancet* 1993; **341**: 72-75

8. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predicts occurrence of osteoporotic fractures. *BMJ* 1996; **312**: 1254-1259

9. Kanis JA Delmas P, Burckhart P, Cooper C, Togerson D. Guidelines for the diagnosis and Management of Osteoporosis. *Osteoporos Int*.1997; **7**: 390-406.

10. Blake GM, Fogelman I: Technical principles of dual x-ray absorptiometry. *Semin Nucl Med* 1997; **27**: 210-228

11. Blake GM, C-C Gluer, Fogelman I. Bone Densitometry: current status and future Prospects. Br *J Rad* 1997; **70**, S177-S186

12. Kung AWC Luk KD, Chu LW, Chiu Pk. *Clinical* Management guidelines for osteoporosis in Hong Kong. *HKMJ* 1998; **4**: 423-31

13. Blake GM, Fogelman I. Interpretation of Bone Densitometry Studies. *Semin Nucl Med* 1997; **27**: 248-260

14. Genant HK: Universal Standardization for dual x-ray Absorptiometry: Patient and phantom cross-calibration results. *J Bone Miner Res* 1994 ; **9**: 1503-1514

15. C-C Gluer, Jergas M, Hans D. Peripheral Measurement techniques for the assessment of osteoporosis. *Semin Nucl Med* 1997; **27**: 229-247

16. Jergas M,C-C Gluer. Assessment of Fracture Risk by Bone Density Measurements. *Semin Nucl Med* 1997; **27**: 261-275

17. Hans D, Dargent-Molina P, Schott AM, Serbert JL, Cormier C, Kotzki PO Delmas PD, Pouilles JM, Breart G, Meunier PJ. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet* 1996; **348**: 511-514

18. Bauer DC, Gluer C-C, Cauley JA. Bone ultrasound predicts fracture strongly and independently of densitometry in older women: A prospective study. *Arch Intern Med* 1997; **157**: 629-634

19. Hans D, Fuerst T, Duboeuf F. Quantitative ultrasound measurement. *Eur Rad* 1997; **7**: S43-S50

20. Schott AM, Hans D, Sornay-Rendu E, Delmas PD, Meunier PJ Ultrasound measurement on os calcis: Precision and age-related changes in a normal female population. *Osteporos Int* 1993; **3**:249-254

21. Gluer C-C. Quantitative Ultrasound Techniques for the Assessment of Osteoporosis: Expert Agreement on Current Status. *J Bone Miner Res* 1997;**12**: 1280-1288

22. Haddaway MJ. Optimal Measurement of bone densitometry in osteoporosis. *Rad Magazine* 1998; **24**:17-18