The diagnosis of osteoporosis and the assessment of fracture risk in postmenopausal women are based primarily on bone mineral density (BMD) criteria. The prevalence of low BMD, the relation between BMD and fracture risk, and the efficacy of treatment to reduce fracture risk are well established in this high-risk (postmenopausal) population. The World Health Organization (WHO) criteria for the diagnosis of osteoporosis and fracture risk, based on BMD, are based on epidemiologic data in postmenopausal women. No such data exist for premenopausal women. The relation of BMD and fracture risk in the latter population is therefore unknown. Moreover, it is inappropriate and inaccurate to extrapolate data from other populations as several other criteria play a key role in determining fracture risk.

With increased availability of and accessibility to Dual X-ray Absorptiometry (DXA) scans, premenopausal women are increasingly either requesting a routine BMD evaluation or are being referred for BMD testing. An understanding of the indications for referral for a DXA scan and the interpretation of a DXA scan in premenopausal women enhances our ability to appropriately manage such patients.

The distribution of BMD at any age is expressed by a bell-shaped Gaussian curve. With ageing and bone loss the mean BMD will decrease and the curve will shift to the left. About 70% of premenopausal women fall within 1 standard deviation (SD) of the mean, and 95% within 2 SD. About 15% have a BMD of more than 1 SD below the mean, and 2.5% of more than 2 SD below the mean. Only 0.6% have a BMD of more than 2.5 SD below the mean. However, the relation between a low BMD and risk of fracture in this population is unclear.

Osteoporosis is defined as “a skeletal disorder characterized by compromised bone strength predisposing to increased risk of fracture”. Bone strength primarily reflects the integration of bone density and bone quality (NIH Consensus Development Panel). No test currently exists to measure bone quality in the individual patient, so BMD is used as the primary measure of bone strength. This is to some extent an accurate measure in postmenopausal women. However, this does not hold true for premenopausal women:

- The official position of the International Society for Clinical Densitometry (ISCD) is that the WHO criteria for the diagnosis of osteoporosis and osteopenia (≤ 1.5 SD osteopenia, ≤ 2.5 SD osteoporosis) should not be applied to healthy premenopausal women. The relation between BMD and fracture risk is not the same and so diagnostic categories and intervention thresholds will also differ. The ISCD states that the diagnosis of osteoporosis in premenopausal women should not be based on DXA scan alone.

- Z-scores, not T-scores, are preferred. This is particularly important in children.

- A Z-score of -2.0 SD or lower is defined as “below the expected range for age” and a Z-score of more than -2.0 SD is “within the expected range for age”.

The significance of bone loss

It is not possible to establish from a single BMD whether low BMD in a premenopausal woman is due to a low peak bone mass (with stable BMD) or whether bone loss has occurred subsequent to the attainment of peak bone mass. Differentiating low peak bone mass (which is the likely scenario for most patients) from bone loss with or without a low peak bone mass is critical.

Bone mass increases dramatically during childhood and adolescence, until peak bone mass (PBM) is reached between the ages of 18 and 35 years. PBM is the amount of bone tissue present at the end of skeletal maturity. Peak bone mass is a major determinant of fracture risk, since the mass of bone tissue present at any time during adult life is the difference between the amount accumulated at maturity.
(PBM) and that lost with ageing. Epidemiological studies indicate that an increase of 10% in peak bone mass in Caucasian women would decrease the risk of fragility fracture by about 50%. Peak bone mass is primarily determined genetically, but environmental factors also play a major role and these are all interdependent.

The metabolic component of bone is made up of Basic Multicellular Units (BMUs), over 1 million of which are active at any given time in a healthy adult. It is estimated that 10% of the skeleton undergoes remodelling at any given time and that turnover of the entire skeleton occurs every 10 years. Bone remodelling is the process by which old bone is replaced by new bone. Remodelling is physiologically essential, because it maintains normal skeletal mass, repairs microdamage, and participates in regulation of systemic calcium homeostasis.

The remodelling balance reflects the difference between the formation phase (osteoblast) and the resorption phase (osteoclast) at the BMU level:

- If the resorption cavity is overfilled by the osteoblasts, the remodelling balance is positive (childhood, adolescence).
- If the resorption cavity is filled normally by the osteoblasts, the remodelling balance is equal (adulthood).
- If the resorption cavity is underfilled by the osteoblasts, the remodelling balance is negative (postmenopause, osteoporosis, ageing).

An imbalance in bone resorption and formation can lead to decreased bone mineral density and microarchitectural deterioration. This would result in a decrease in bone strength and predisposition to fracture.

**Indications for fracture risk assessment in premenopausal women**

BMD assessment should be done based on clinical criteria as these criteria will largely influence treatment decisions. A routine DXA scan should not be done on all patients with positive family history, as part of a routine medical assessment, as a population screening strategy or in patients with minor risk factors (smoking, low body mass index but still menstruating). If the DXA scan will not influence treatment decisions, this author’s opinion is: don’t do it.

The ISCD suggests the following indications for performing a DXA scan in premenopausal women:

1. Fragility fracture
2. Disease, condition, or medication associated with low bone mass or bone loss (see Table I)
3. Pharmacologic treatment for osteoporosis being considered
4. Monitoring effect of treatment in a given patient

**Full fracture risk assessment**

A full fracture risk assessment aims to address two questions. The first aim is to identify a secondary cause for bone loss or low bone mass, and the second aim is to try to identify the small percentage of patients who require bone-specific treatment.

The assessment of fracture risk is based on a combination of a thorough history and examination followed by appropriate laboratory and radiological tests. Premenopausal patients with low bone mass will have a higher than expected incidence of secondary causes for low bone mass. A thorough assessment is therefore mandatory. The clinical approach to such patients is outlined in Table II. “Special laboratory” tests should be done only in selected patients based on clinical criteria.

In the opinion of this author, bone turnover markers play an important role in treatment decisions. Elevated markers suggest that the patient is experiencing bone loss and that bone-specific treatment may be necessary.

**Table I: Risk factors for osteoporosis in premenopausal women**

| Inherited | Nutritional | Metabolic/Endocrine | Medication | Others |
|-----------|-------------|---------------------|------------|--------|
| Osteogenesis imperfecta | Malabsorption | Hyperparathyroidism | Glucocorticoids | Multiple myeloma |
| Homocysteinuria | Liver disease | Thyrotoxicosis | Antibiotics | Rheumatoid arthritis |
| Marfan syndrome | Alcoholism | Cushing’s syndrome | Heparin | Mastocytosis |
| Connective tissue diseases | Calcium deficiency | Anorexia nervosa | Thyroid hormone excess | Immobilisation |
| | Vitamin D deficiency | Hyperparathyroidism | Depo-Provera | Idiopathic hypercalcemia |

**Table II: Clinical evaluation of the premenopausal patient**

| History | Examination | Laboratory | Radiology | Special laboratory |
|---------|-------------|------------|-----------|--------------------|
| Family history | Height | Full blood count | Lateral X-ray spine or VFA | Protein electrophoresis |
| Previous fractures | Weight | Urea and electrolytes | DXA scan | Serum 25(OH) vitamin D |
| Height loss | Body Mass Index | Ionised calcium | Coeliac antibodies |
| Age at menarche | Nutritional status | Phosphate | Prolactin |
| Amenorrhoea | Proximal muscle power | Parathyroid hormone | 24-hour urine cortisol |
| Eating disorders | Arthropathy | TSH |
| Nutrition | Blue sclera | 24-hour urine calcium | Bone turnover markers |
| Smoking | Signs of Cush- ing’s syndrome | Estradiol |
| Alcohol | Thyroid enlarge- ment | FSH |
| Contraception | Thyrotoxicosis |
| Malabsorption | Secondary sexual characteristics |
| Thyroid disease | Signs of Turner Syndrome |
| Glucocorticoid use | Kyphosis |
| Heparin use |
| Anti-epilepsy medication |
| Previous X-rays |
| Previous DXA scans |
| Diabetes mellitus |
Protocol 1: Patient has had a DXA scan and is referred for “evaluation and treatment”

Protocol 2: Patient referred for a DXA scan for “osteoporosis assessment”
Treating the patient with premenopausal osteoporosis

A conservative approach to treatment is appropriate for the vast majority of patients. This includes information on appropriate diet with adequate protein and calcium and advice to quit smoking and limit alcohol to one unit a day. Calcium and vitamin D supplementation as well as regular weight-bearing exercise has been shown to benefit bone mineral density. No effect on fracture risk has been demonstrated in this age group.

Diseases, medications and secondary causes of bone loss must be identified and treated where possible. Patients with coeliac disease have been shown to have large increases in BMD and reductions in bone markers when on a gluten-free diet. Several causes of vitamin D deficiency are known, including skin covering (clothing in religious sects, sunscreen) and anticonvulsant use, which may impair hepatic vitamin D metabolism. Vitamin D supplementation will cure the mineralisation deficit in such patients with concomitant improvement in BMD and bone markers. Chronic glucocorticosteroid use at any age may be associated with precipitous bone loss and in 50% of cases fracture, in particular vertebral fracture. Patients taking oral glucocorticosteroids at doses of 5 mg or more for three months or longer must be assessed for fracture risk and treatment should be offered if appropriate. Bisphosphonates are the treatment of choice, but should be used with caution. The long-term effects of these agents are not known and several recent papers have highlighted the possibility of oversuppression of bone remodelling and risk of subtrochanteric femur fracture.

Low-dose oral contraceptives have been prescribed to treat mainly patients with eating disorders and low bone mass. The effect on BMD is unclear and there is no convincing evidence that this is of benefit.

For the vast majority of premenopausal patients with low BMD, there is no evidence that bone-specific treatment has beneficial effects on BMD or reduces fracture risk. No long-term fracture, BMD or safety data is available with any of the agents used to treat osteoporosis in this population.

Better clinical tools are required to identify those patients with impaired bone quality in addition to low bone mass who are at high risk of fracture. Such patients would be possible candidates for pharmacologic treatment to reduce fracture risk. Safety and efficacy studies with pharmacologic therapy are lacking, and all agents should therefore be prescribed with caution. Patients should be re-evaluated regularly and management decisions reviewed.

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