Review Article

Premenopausal osteoporosis

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ABSTRACT

Osteoporosis has traditionally been considered a disorder of postmenopausal women, but low bone mass and accelerated bone loss can also occur early in life causing premenopausal osteoporosis. There are a few risk factors that increase a woman's risk of premenopausal osteoporosis, including drugs, hormonal and nutritional factors, and physical in-activity, which need to be identified and managed accordingly. Lifestyle modification is of importance in preventing progressive bone loss in premenopausal women and should be actively encouraged.

Key words: Bone mineral density, osteoporosis, premenopausal osteoporosis

A 36-year-old Chinese female consulted her general practitioner complaining of a month's history of right foot pain. There was no history of trauma, fever or any precipitating cause. A radiograph of her right foot revealed a fracture in the head of the third metatarsal.

She had always been of average height and weight, and never exercised excessively. Menarche occurred at the age of 13 and menses were regular. She did not smoke, drink alcohol, or take on any regular medication. Nor did she have any eating disorders.

On physical examination, she was 1.55 m tall and weighed 50 kg, with a body mass index (BMI) of 20.8 kg/m^2. She was not clinically cushingoid or thyrotoxic. In view of the spontaneous fracture, she was worked up for possible osteoporosis.

A bone mineral density (BMD) scan was done which revealed the following results [Figure 1; Table 1].

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.109681

Biochemical tests confirmed normal renal, liver, and thyroid function. Calcium levels, erythrocyte sedimentation rate (ESR), myeloma panel, luteinizing hormone (LH), follicular stimulating hormone (FSH), estradiol, and prolactin were all within normal ranges. An overnight dexamethasone suppression test revealed normal cortisol suppression at 13 nM. Parathyroid hormone (PTH) level was normal at 4.7 pM, with normal 24-hour urinary calcium at 2.10 mmol/day.

She was advised to undertake weight-bearing exercise regularly and have a diet rich in calcium. As secondary causes of osteoporosis were not found and she was still of child-bearing age, bisphosphonates were not initiated. She was monitored regularly in the clinic, and remains well without further fractures.

Discussion

Diagnosis and assessment

Osteoporosis is a chronic progressive disease characterized by low bone mass, micro-architectural bone deterioration, and decreased bone strength that lead to increased bone fragility and a consequent increase in fracture risk.[1] The World Health Organization (WHO) came up with definitions of osteoporosis and osteopenia in postmenopausal white women based on BMD to help physicians classify degrees of bone loss.[2] In current clinical practice, the diagnosis of osteoporosis is based on either a health outcome like a fragility fracture, or an intermediate outcome like a low BMD.[2]

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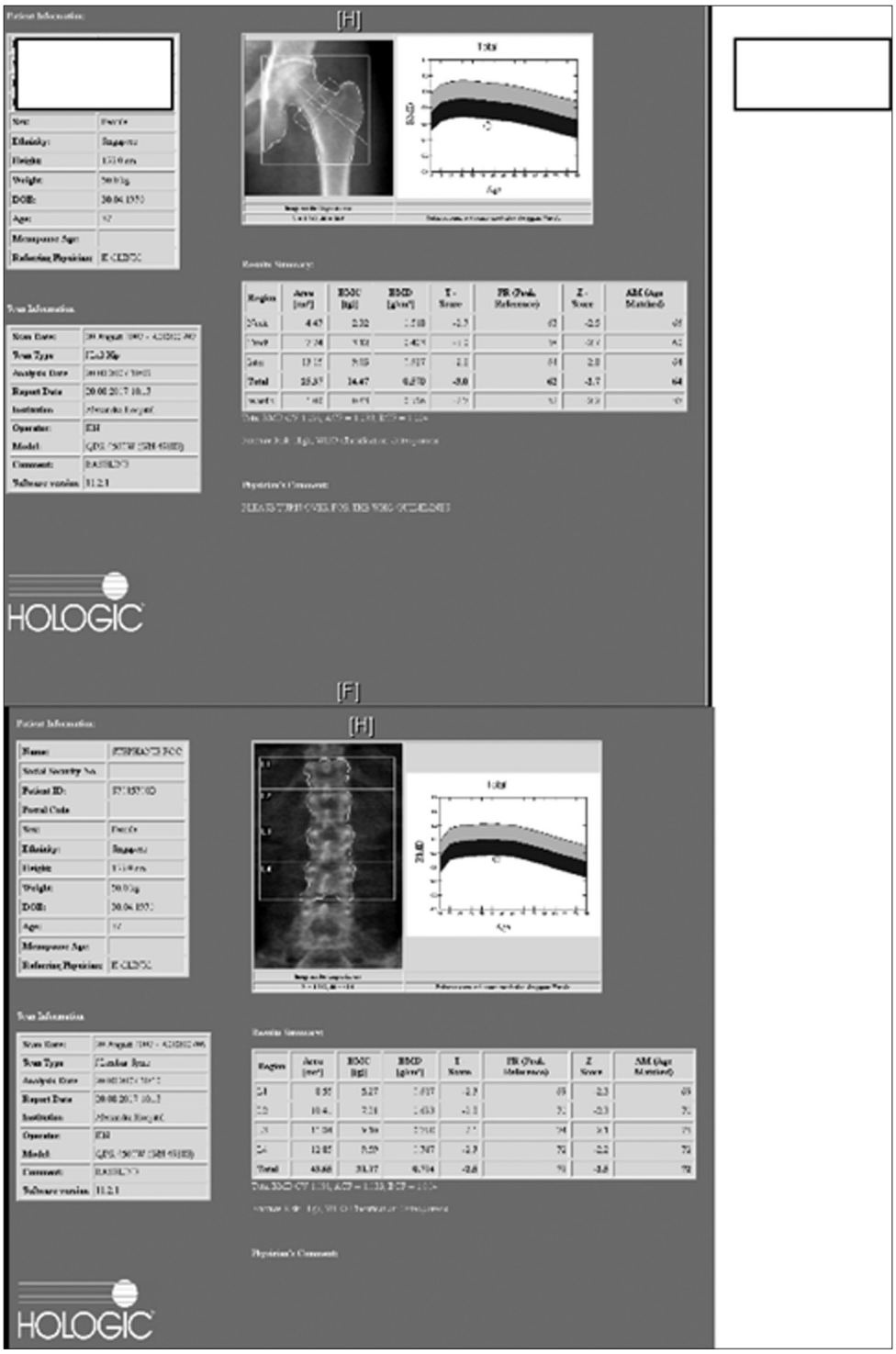

Figure 1: Bone mineral density results

Table 1: BMD results (Hologic Machine)

BMD	Lumbar spine	Neck of femur
T score	-2.5	-3.0
Z score	-2.5	-2.7

Osteoporosis is generally considered a disorder of postmenopausal women, but low bone mass and accelerated bone loss can also occur early in life and contribute to pre-menopausal osteoporosis.[3] Certain groups of premenopausal women are at higher risk of osteoporosis than their peers, and these include women with disease states like primary hyperparathyroidism, Cushing's syndrome, and thyrotoxicosis, that promote accelerated bone loss.[3]

Premenopausal osteoporosis is defined as low bone mineral density (a Z score below -2.0) in combination with risk factors

such as chronic malnutrition, eating disorders, hypogonadism, glucocorticoid exposure, and previous fractures.[4]

Peak bone mass occurs before the age of 30. Longitudinal studies have shown that calcium utilization increases during early puberty[5] and that the highest rates of calcium accrual may occur at a mean age of 12.5 years in girls and 14 years in boys.[6] Factors affecting the attainment of peak bone mass include genetic background, nutritional status, and activity level.[3] Family studies have shown that 50--80% of variance in bone mass is heritable.[7]

Bone mineral density follows a normal distribution, and low bone density, defined as a T-score of less than 1.0 standard deviation below the young adult mean is present in about 15% of young, healthy women aged between 30 and 40 years.[8] Around 0.5% of these women have a T-score of less than or equal to -2.5. Currently, there are insufficient data regarding the relationship between BMD and fracture risk in the premenopausal female population. Therefore, it is not possible to make recommendations regarding the appropriate BMD criteria for a diagnosis of osteoporosis in premenopausal women in the absence of secondary causes.[9] The WHO definition of osteoporosis based on a T-score cut-off point of -2.5 is applicable only to the postmenopausal female and cannot be applied to the premenopausal female in the absence of secondary causes of bone loss.

Low peak bone mass without the presence of fragility fractures or height loss may be reflective of the normal variation in BMD.[9] This may not be associated with increased fracture risk in premenopausal women.[8]

Risk factors

Risk factors of premenopausal osteoporosis include the following: genetic influences, ethinicity, hormonal influences, nutritional factors, physical activity, disease factors, medications, and smoking.[3] Racial and ethnic differences in BMD values have been reported, and population norms have been established for use as DXA reference standards.[10] Bone loss can also occur due to prolonged amenorrhea and estrogen deficiency. In a study of 200 women, aged 16 to 40 with 6 months to 24 years of amenorrhea, it was found that lumbar spine BMD was 15% lower compared to 57 age matched controls.[11] As estrogen has antiresorptive properties in bone, it is thought that oral contraceptive (OC) use can increase bone mineral density. However, prospective studies on OC use in premenopausal women failed to show consistent gains in BMD.[3] Progestational agents used for contraception in premenopausal women can cause bone loss due to the associated oestrogen deficiency.[9] Increased calcium intake is generally recommended in osteoporosis. In studies looking at the association of BMD and calcium intake in healthy premenopausal women, statistically significant correlations were found between calcium intake and BMD at three femoral sites.[12]

Osteoporosis is a prevalent complication in patients with anorexia nervosa. This is prevalent in female athletes as they have a higher incidence of eating disorders than their peers and are at a much higher risk of stress fractures.[4] In a cohort study of 56 women with eating disorders, it was found that the BMD in the femur of these women were below the critical fracture threshold in 75% of patients.[13] The factors involved include estrogen deficiency and resultant amenorrhea,[14] Leptin levels are usually low in patients with anorexia nervosa, and may have an effect on IGF-1, especially in low body weight states.[15] Physical activity has been shown to increase BMD. A longitudinal study was done to examine the BMD of the lumbar spine and femur in premenopausal caddies and desk workers. The change in BMD was significantly better in the caddies than desk workers, suggesting that regular intense activity resulted in gain in BMD.[16]

Medications can also contribute to premenopausal osteoporosis. Glucocorticoids are commonly used in the treatment of many conditions, including inflammatory and autoimmune diseases. Glucocorticoid induced osteoporosis is the most common cause of drug-induced osteoporosis, and occurs as a result of decreased bone formation secondary to impaired osteoblastic differentiation and function. [17] Many psychotropic and anticonvulsant medications may also alter skeletal metabolism. Selective serotonin reuptake inhibitors (SSRI) can cause bone loss by affecting functional serononin receptors and transporters that are present in osteoblasts and osteocytes. Anticonvulsants accelerate the metabolism of vitamin D and may also have direct inhibitory effects on osteoblast differentiation.[18] Smoking has also been reported to significantly lower BMD. Two meta-analyses[19,20] have reported significant lowering of BMD at the hip in long term smokers compared to nonsmokers.

Idiopathic premenopausal osteoporosis

Although most young people with osteoporosis have an identifiable cause, some may have idiopathic osteoporosis in which no etiology can be found.[21] This has been variably defined in the literature and most of the reported cases are in Caucasians, with the usual clinical history being one of multiple atraumatic fractures, involving mainly cancellous bone.[22] A retrospective study[21] on young healthy women who presented with fragility fractures was carried out who had trans-iliac bone biopsies undertaken as part of their evaluation. All secondary causes of osteoporosis were excluded by means of history taking, physical examination

and biochemical testing. This was compared to age, sex, and race-matched healthy controls. It was demonstrated that women with idiopathic osteoporosis had evidence of decreased bone formation and altered bone resorption. These abnormalities were most prominent in cancellous bone. Thus, it was concluded that women with idiopathic osteoporosis have uncoupling of resorption and formation, as well as osteoblast dysfunction.

Management

Management should start with lifestyle intervention. Weight bearing exercises, adequate nutrition and calcium intake, smoking cessation as well as maintenance of a normal body mass index are of value in maintaining BMD.[23] Offending medications should be stopped, if at all possible.

Correction of the secondary cause should be undertaken as soon as it is diagnosed. This may be associated with significant improvement in BMD and reduction in fracture risk. Antiresorptive therapy has only been evaluated in premenopausal women receiving glucocorticoid therapy or in secondary causes of bone loss such a primary hyperparathyroidism.[9] There are no data regarding the use of bisphosphonates in the treatment of premenopausal osteoporosis in the absence of these secondary causes. In women who are oestrogen replete who have normal bone turnover, bisphosphonates may be harmful as they have long term skeletal and may have adverse effects on future pregnancies.[9] They have been shown to pass through the placenta in animal studies and accumulate in the fetus,[24] and their effects on the developing fetal skeleton are still unknown. Hence, bisphosphonates should be limited in premenopausal women until further research is done to clarify its safety and efficacy.

Screening

The National Osteoporosis Foundation[25] states that the current available data are insufficient to formulate specific recommendations for premenopausal women. Premenopausal women with disease states associated with accelerated bone loss should be managed on a case-by-case basis. The advantages of early detection have to be weighed against the risk of potential harm, including treatment associated morbidity.[1]

Conclusion

Low bone mass density in premenopausal women warrants further evaluation and secondary causes should be sought for and treated. Antiresorptive therapy has only been evaluated in premenopausal women receiving glucocorticoids or in secondary causes of bone loss such as primary hyperparathyroidism, and should be used with caution in premenopausal women because of the lack of safety data for future pregnancies. Lifestyle modification is of value in preventing progressive bone loss in premenopausal women and should be actively encouraged.

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Cite this article as: Cheng ML, Gupta V. Premenopausal osteoporosis. Indian J Endocr Metab 2013;17:240-4.

Source of Support: Nil, **Conflict of Interest:** None declared.