Review Article

Indian J Med Res 127, March 2008, pp 263-268

Osteoporosis in Indians

N. Malhotra & A. Mithal

Department of Endocrinology & Diabetes, Indraprastha Apollo Hospital
New Delhi, India

Received October 5, 2007

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhance bone fragility, thus increasing the susceptibility to fracture. Although exact numbers are not available, based on available data and clinical experience, on estimated 25 million Indians may be affected. Osteoporotic fractures in India occur commonly in both sexes, and may occur at a younger age than in the West. Recently published data have clearly demonstrated widespread vitamin D deficiency across India, at all ages and in both sexes, particularly in the urban areas. Poor sunlight exposure, skin pigmentation and a vitamin D-deficient diet are some obvious causes for this finding. Indians have low BMD as compared to the western Caucasians. This could be attributed to differences in skeletal size; however, the high prevalence of vitamin D deficiency is a major factor in the low BMD and poor bone health of Indians. Healthy lifestyle (diet, exercise and sunlight exposure) can have a major positive impact on the bone metabolism and bone health of Indians. These public health measures are recommended for the population at large as they are efficacious, safe and cost-effective. The peak bone mass of the population can be increased significantly by appropriate and timely intervention in children. Pharmacological interventions are expensive and should therefore be targeted to only those at high risk of fractures.

Key words Bone mineral density - calcium - fracture - osteoporosis - peak bone mass - vitamin D

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhanced bone fragility. This increases the susceptibility to fracture. Osteoporosis is a silent disease, reflected only in a low bone density, till a fracture occurs. Much in the manner that asymptomatic conditions such as hypertension and dyslipidaemia predispose to stroke and myocardial infarction, respectively, a low bone density (reflecting poor bone health) predisposes to osteoporotic fractures. With increasing longevity of the Indian population, it is now being realized that, as in the West, osteoporotic fractures are a major cause of morbidity and mortality in the elderly. Based on 2001 census, approximately 163 million Indians are above the age of 50; this number is expected to increase to 230 million by 2015[1]. Even conservative estimates suggest that of these, 20 per cent of women and about 10-15 per cent of men would be osteoporotic. The total affected population would, therefore, be around 25 million. If the lower bone density is shown to confer a greater risk of fracture, as is expected, the figure can increase to 50 million[2].

During puberty and adolescence, the skeleton takes up calcium avidly and builds up its reserves. This uptake

of calcium into the bone is largely dependent on calcium and vitamin D nutrition, as well as exercise. Peak bone mass is usually achieved by the age of 30 yr. From the mid-thirties there is a gradual, progressive bone loss, which continues throughout life and is accelerated at the menopause in women. The fracture prevention strategy therefore consists of increasing peak bone mass in the growing years and reducing subsequent bone loss throughout life. Thus, the importance of achieving and maintaining good bone health cannot be overemphasized.

Epidemiology

Although reliable epidemiological data are lacking, hospital data suggest that hip fractures are common in India. Data also suggest that men are probably more commonly affected than women, although this may be because the likelihood of men seeking hospital attention is greater than that for women. Almost four decades ago, Nordin reviewed 119 hip fractures and found that, in India, they occured at all ages, with two peaks at 30-39 yr and again at 50-70 yr. There was no attempt to distinguish traumatic from fragility fractures[1]. Around the same time, Gupta *et al*[2] from Kanpur analyzed 425 hip fractures, 63 per cent of which were in men. The average age at fracture was 49 yr in men and 57 yr in women, and combined average age was 55 yr[2]. Vaishnava & Rizvi[3] found osteoporosis based on iliac crest biopsies in 141 out of 421 hip fracture patients, and again more than half their patients were men. Indians living in Singapore were also found to have hip fractures at an average age of 58 yr[4]. More recent data from Sankaran[5], involving 1393 patients of hip fractures from 3 large Delhi hospitals, also indicated that these fractures were common in both sexes, although the sex ratio in different subgroups was variable, and not always in favour of men. The peak age at which these fractures occurred was 60-70 yr. In western countries, women suffering from osteoporosis far outnumber men, and this is largely thought to be due to the effects of the menopause[8].

There are no epidemiological data on fracture prevalence, although most clinicians would agree that hip fractures are common. The men: women ratio may be distorted because men are more likely to be brought for hospital care. The lower peak age as compared to the West may simply be linked to a shorter life span, as also to the inclusion of traumatic/ non-fragility fractures in the analysis. Perhaps it is true that osteoporotic fractures are common in India and occur in both sexes.

Pathogenesis

The pathogenesis of osteoporosis is complex. In childhood and adolescent period bone formation exceeds resorption, resulting in continued skeletal growth and denser, longer and heavier bones. This process slows down in adulthood, and peak bone mass is attained at about 30 yr of age. After this, resorption begins to exceed formation. Normal bone loss averages 0.7 per cent per year. It gets accelerated at the time of menopause to 2-5 per cent per year, which may continue for up to 10 years. Since cancellous bone is much more metabolically active than cortical bone, in periods of accelerated bone loss cancellous bone loss is 3-fold greater. Osteoporotic fractures, therefore, commonly occur in vertebrae. Peak bone mass is primarily determined by genes but may be modified to a considerable extent by certain factors like physical activity, calcium, vitamin D nutrition, smoking, alcohol, concurrent illnesses, and medications (glucocorticoids, antiepileptics)[9]. The level of peak bone mass achieved at puberty is a major determinant of bone mass in later life and hence an important factor in the ultimate development of osteoporosis.

Risk factors

Human beings of all races and ethnicity are prone to osteoporosis and fracture. It has been shown that blacks have greater and Asians have lower bone mass than whites. Several risk factors contribute to low bone mass. These include non-modifiable factors like female sex, old age, small thin built, Caucasian/Asians and family history of fractures. Ethnic differences in bone mineral density (BMD) are strongly influenced by body weight. Important modifiable risk factors include calcium and vitamin D deficiency, sedentary life style, smoking, excessive alcohol and caffeine intake. A case control interview based study on postmenopausal women showed history of fracture in relatives, weight <60 kg, height <155 cm as significant risk factors for osteoporosis and regular consumption of milk, almonds, fruits as protective factors[6]. A similar interview based study on patients admitted with hip fracture revealed calcium intake, increased body mass index (BMI) and higher activity levels to have a significant protective effect on hip fracture in urban north Indian population. On the other hand excessive caffeine intake and decreased agility increase the risk of hip fracture[7].

Medical conditions like hypogonadism, thyrotoxicosis, Cushing syndrome, anorexia nervosa,

malabsorption syndromes, chronic liver and renal disease, drugs like glucocorticoids and anticonvulsants, and chronic inflammatory conditions like rheumatoid arthritis may lead to secondary osteoporosis.

Aetiology

Genetic factors: Studies have suggested that a major genetic component responsible for bone mass may be linked to polymorphism in the gene for vitamin D receptor (VDR)[8]. Advances made in the genetics of osteoporosis may have implications for racial differences in the clinical spectrum of disease. Since *VDR* gene may be a determinant of bone mass, differences in *VDR* gene polymorphism in different races could account for differences in bone mass. Polymorphism of the alleles of the vitamin D receptor gene may account for the major part of the heritable component of bone density in women, possibly mediated in part by impaired calcium absorption from the bowel but this association has not been found in group of men[9]. A recent study by Mitra *et al*[10] also revealed that *VDR* gene polymorphisms were associated with BMD in postmenopausal Indian women and may influence determinants of bone metabolism. Another study done by Vupputuri *et al*[11] reported that variation in BMD at spine and forearm was related to parathyroid hormone levels and *VDR* gene polymorphisms and at hip to vitamin D deficiency in vitamin D deficient/ insufficient urban Asian Indians. In addition, estrogen receptor α (ERα) gene polymorphisms may also be associated with BMD in Indian women and may influence some determinants of bone metabolism resulting in accelerated age related bone loss[12].

Nutritional factors: Calcium and vitamin D nutrition plays an important role in determining bone health. Recent data demonstrated a high prevalence of vitamin D deficiency in different subgroups of Indian population, despite the availability of abundant sunshine. This includes both urban and semi-urban Indians, postmenopausal women, pregnant women, school children and newborns[13-16]. Studies have shown that the majority of urban office workers and hospital staff have moderate to severe vitamin D deficiency, which is usually asymptomatic[17,18]. Arya *et al*[18] used a serum 25(OH) vitamin D level of 15 ng/ml as a cut-off, and found 66.3 per cent of subjects to be vitamin D deficient. Of these, 20.6 per cent had severe vitamin D deficiency (<5 ng/ml), 27.2 per cent had moderate (5-9.9 ng/ml) while 18.5 per cent had mild vitamin D deficiency (10-14.9 ng/ml). When a serum 25(OH) vitamin D level of 20 ng/ml was used as a cut-off, 78.3 per cent subjects were diagnosed to be vitamin D deficient/insufficient. The serum 25(OH) vitamin D level correlated with sunlight exposure and femoral neck BMD. Inadequate calcium intake was proposed as an additional factor contributing to the low BMD. This was shown in a study by Shatrugna *et al*[19] on Indian women from low income groups who consume diets that have inadequate calcium coupled with too few calories, proteins and micronutrients. BMD and T scores at all the skeletal sites were much lower than the values reported from the developed countries and were indicative of a high prevalence of osteopenia and osteoporosis. Body weight, age, menopause and calcium intake were found to be important determinants of BMD[19]. Tandon *et al*[20] reported their findings on the bone health of Indians with optimal vitamin D availability. Their subjects were healthy young adults, both men and women, from the Indian paramilitary forces. They consumed a nutritious, balanced diet, with average calcium intakes of over 750 mg/day in women and 1000 mg/day in men. They performed regular physical exercise and had adequate exposure to sunlight. The authors reported a serum 25(OH) vitamin D level of 18.4 ng/ml in winter and 25.3 ng/ml in those studied in summer. These levels were much higher than those reported in previous studies from India[17-21], which is probably related to greater exposure to sunlight in this study population. Although the sample size was small, the differences in BMD as compared to western controls were also less than those reported earlier. The minor differences in BMD could possibly be related to lower peak bone mass attained during puberty, since these subjects were recruited to the service after18 yr of age. The study is of importance because it has shown that a healthy lifestyle (diet, exercise and sunlight exposure) can have a major positive impact on the bone metabolism and bone health of Indians.

Thus, low vitamin D level (and low calcium intake) seems to be a major contributing factor to poor bone health and osteoporosis in India. Poor sunlight exposure, skin pigmentation and vitamin D-deficient diet are some obvious causes for this finding. Atmospheric pollution has also been suggested as a contributor to vitamin D deficiency in children from Delhi[21]. Low serum 25(OH) vitamin D levels have also been reported in expatriate Indians from the UK and USA[22]. Lo *et al*[8] showed that Indian and Pakistani immigrants in the USA have the same capacity to produce vitamin D in response to ultraviolet light though longer exposure to sunlight is

required. One study reported altered vitamin D metabolism in cultured skin fibroblasts from Indians[23].

The spectrum of vitamin D deficiency in India extends from asymptomatic deficiency, described above, to frank osteomalacia, a crippling disorder, which continues to be seen, even in 'tertiary care' corporate hospitals[24]. Another reflection of the poor bone health of Indians is the severe bone disease seen in Indians with primary hyperparathyroidism, who have consistently been shown to have low serum levels of 25(OH) vitamin D[25]. On the contrary, vitamin D replete 'western' patients of primary hyperparathyroidism typically have no symptoms at all and diagnosed on routine laboratory screening for serum calcium level.

Diagnosis

Dual energy X-ray absorptiometry (DEXA) technology, the gold standard for diagnosing osteoporosis by measuring bone density, became available in India only in 1997 at the Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. Subsequently, several other hospitals/institutions acquired this and the past couple of years have seen their number grow to almost 200, and with increasing spread to middle sized towns. Thus, while certain segments of the Indian population do have access to diagnosis and treatment, these techniques remain inaccessible to the majority of Indians. The most important question in this regard is the appropriateness (or otherwise) of western standards for diagnosing osteoporosis in Indians. Single-centre studies on BMD in Indians (from Lucknow, Delhi, Bangalore, Chennai) using DEXA have consistently shown a lower BMD in Indian women[31-35]. Overall, the BMD at all sites seems to be 5-15 per cent lower than that in Caucasians[26-30]. However, there are differences in BMD between different centers, and a study involving healthy subjects presenting for a preventive health check in Delhi has suggested that differences with western populations in BMD may be minimal, and could be related to the smaller skeletal size of Indians[31]. Studies on expatriate Indians, although on a limited number of subjects, have also shown a lower BMD as compared to that in Caucasians[32,33]. This could reflect just differences in skeletal size, or genetic differences, or may actually reflect poor bone health resulting from nutritional issues, as described above. The issue of appropriate BMD normative data for Indians remains open. There is a need to study the BMD-fracture relationship in Indians (fracture threshold) to determine the ideal normative data for the Indian population[34]. If Indians fracture at the same level of BMD as Caucasians, there would be no reason to have separate normative data for Indians.

Treatment

Universal public health measures (calcium/vitamin D/ exercise) are recommended in all patients regardless of BMD, as they are efficacious, safe and cost-effective. Pharmacological interventions are expensive and should therefore be targeted to those at high risk of fractures. Vitamin D deficiency induced osteomalacia is very common. Therefore, all patients should undergo investigations for it by getting serum levels of calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (PTH) measured. Osteomalacia if present, should be treated first. If vitamin D deficiency is a major contributor to the low bone density very striking rises in bone density can be observed with calcium/ vitamin D supplementation[25,32].

Pharmacological agents are classified into anticatabolic (bisphosphonates, raloxifene, estrogen, calcitonin) and anabolic agents (teriparatide) depending on their effects on bone remodeling and with respect to the mechanisms of fracture reduction. The lack of direct head to head trials of treatments for osteoporosis, with reduction in fractures as an end point, makes it difficult to determine the relative efficacy of the different treatments. When deciding the treatment, aspects like individual values, absolute risk of fracture, extraskeletal effects, and costs need to be considered. If the goal is to decrease risk of vertebral fractures, then the choices would include raloxifene or bisphosphonates in mild cases. Bisphosphonates (alendronate, risedronate or ibandronate) are clearly the drugs of choice in the usual moderate to severe cases. If the goal is to reduce the risk of vertebral and non vertebral fractures, then bisphosphonates would be the automatic choice, but for those with severe osteoporosis especially with pre-existing fracture, teriparatide would be the preferred option. The role of calcitonin has gradually declined with the availability of newer agents, while strontium still needs further evaluation, particularly in the Indian setting.

Conclusion

It appears that overall, Indians have poor bone health, and osteoporosis is common in India. Peak bone mass achieved during puberty is a strong predictor of development of osteoporosis in later years. High prevalence of vitamin D deficiency in India is a major

contributor to low bone mass. As a public health measure, it is important to encourage children to drink milk and play in the sun. This will ensure adequate calcium intake, vitamin D synthesis, and exercise. These three are the crucial elements in determining peak bone mass. There is thus an urgent need for greater public awareness in this regard. For the middle aged and elderly, early detection and treatment of osteoporosis with available agents can significantly reduce the risk of fractures and associated morbidity and mortality.

References

1. Nordin BEC. International patterns of osteoporosis. *Clin Orthop* 1966; *45* : 17-30.
2. Gupta AK, Samuel KC, Kurian PM, Rallan RC. Preliminary study of the incidence and aetiology of femoral neck fracture in Indians. *Indian J Med Res* 1967; *55* : 1341-8.
3. Vaishnava H, Rizvi SNA. Frequency of osteomalacia and osteoporosis in fractures of proximal femur. *Lancet* 1974**;** *1* : 676-7.
4. Wong PCN. Femoral neck fractures among major racial groups in Singapore: Incidence pattern compared with new Asian communities. *Singapore Med J* 1964; *5* : 150-4.
5. Sankaran B. Clinical studies: Incidence of fracture neck of femur and intertrochanteric fractures in three Delhi hospitals. In: Sankaran B, editor. *Osteoporosis*. New Delhi: South East Asia Regional Office, World Health Organization; 2000. p. 9-18.
6. Keramat A, Mithal A. Risk factors for osteoporosis in urban Asian Indian women presenting for a preventive health check-up. 2nd Joint Meeting of the European Calcified Tissue Society and the International Bone and Mineral Society, Geneva, 2005, June 25-29.
7. Jha R, Mithal A, *et al*. Pilot case control investigation of risk factors for hip fractures in the urban Indian population. 2nd Joint Meeting of the European Calcified Tissue Society and the International Bone and Mineral Society, Geneva, 2005, June 25-29.
8. Lo CW, Paris PW, Holick MF. Indian and Pakistani immigrants have the same capacity as Caucasians to produce vitamin D in response to ultraviolet irradiation. *Am J Clin Nutr* 1986; *44* : 683-5.
9. Francis RM, Harrington F, Turner E, Papiha SS, Datta HK. Vitamin D receptor gene polymorphism in men and its effect on bone density and calcium absorption. *Clin Endocrinol* 1997; *46* : 83-6.
10. Mitra S, Desai M, Ikram M. Vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal Indian women. *Maturitas* 2006; *55* : 27-35.
11. Vupputuri M, Goswami R, Gupta N, Ray D, Tandon N, Kumar N. Prevalence and functional significance of 25-hydroxyvitamin D deficiency and vitamin D receptor gene polymorphisms in Asian Indians. *Am J Clin Nutr* 2006; *83* : 1411-9.
12. Mitra S, Desai M, Ikram M. Association of estrogen receptor α gene polymorphisms with bone mineral density in postmenopausal Indian women. *Mol Genet Metab* 2006; *87* : 80-7.
13. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr* 2005; *81* : 1060-4.
14. Marwaha R, Tandon N, Reddy DR, Aggarwal R, Sawhney RC, Saluja B, *et al*. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* 2005; *82* : 477-82.
15. Harinarayan CV. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. *Osteoporosis Int* 2005; *16* : 397-402.
16. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao P, Sarma KVS, *et al*. High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians. *Am J Clin Nutr* 2007; *85* : 1062-7.
17. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25 hydroxyvitamin D concentrations in healthy subjects in Delhi. *Am J Clin Nutr* 2000; *72* : 472-5.
18. Arya V, Bhambri R, Godbole MM, Mithal A. Vitamin D status and its relationship with bone mineral density in healthy Asian Indians. *Osteoporosis Int* 2004; *15* : 56-61.
19. Shatrugna V, Kulkarni B, Kumar PA, Rani KU, Balakrishna N. Bone status of Indian women from a low-income group and its relationship to the nutritional status. *Osteoporosis Int* 2005; *16* : 1827-35.
20. Tandon N, Marwaha RK, Kalra S, Gupta N, Dudha A, Kochupillai N. Bone mineral parameters in healthy young Indian adults with optimal vitamin D availability. *Natl Med J India* 2003; *16* : 298-302.
21. Puliyel JM, Agarwal K, Upadhyay P, Mawer EB, Berry JL, Mughal Z. The impact of atmospheric pollution related haze on vitamin D status of two-year olds in Delhi, India. *J Bone Miner Res* 2000; *15* (Suppl 1) : S356.
22. Sheran E, Newton O, Ali HA, Walford S, Singh BM. Prevalence of hypovitaminosis D in Indo-Asian patients attending a rheumatology clinic. *Bone* 1999; *25* : 609-61.
23. Awumey EMK, Mitra DA, Hollis BW, Kumar R, Bell NH. Vitamin D metabolism is altered in Asian Indians in the southern United States: A clinical research centre study. *J Clin Endocrinol Metab* 1998; *83* : 169-73.
24. Bhambri R, Naik V, Malhotra N, Taneja S, Rastogi S, Mithal A. Change in bone mineral density following treatment of osteomalacia and rickets. *J Clin Densitometry* 2006; *9* : 120-7.
25. Rao DS, Agarwal G, Talpos GB, Phillips ER, Bandeira F, Mishra SK, *et al*. Role of vitamin D and calcium nutrition in disease expression and parathyroid tumor growth in primary hyperparathyroidism: A global perspective. *J Bone Miner Res* 2002; *17* (Suppl 2) : N75-N80.
26. Mithal A, Nangia S, Arya V, Verma BR, Gujral RB. Spinal bone mineral density in normal Indian females. *J Bone Miner Res* 1998; *13* (Suppl 1) : S591.
27. Reddy PG, Mithal A, Rao DS. Bone mineral density in healthy Asian Indian women: Development of a reference database

and implications for diagnosis of osteoporosis in Indian women living in the United States. *J Bone Miner Res* 2002; *17* (Suppl 1) : SA270.

28. Ravishankar U. Bone mineral density in normal Indian women: Assessment by dual energy X-ray absorptiometry. In: Sankaran B, editors. *Osteoporosis*. New Delhi: South East Asia Regional Office, World Health Organization; 2000. p. 20-2.
29. Dharmalingam M, Prasanna Kumar KM, Patil J, Karthikshankar S. Study of bone mineral density in postmenopausal women. *Bone* 2003; *32* (Suppl) : S178.
30. Anburajan M, Rethinasabapathi C, Korath MP, Ponnappa BG, Kumar KS, Panickar TM, *et al*. Age-related proximal femur bone mineral loss in South Indian women: A dual energy X-ray absorptiometry study. *J Assoc Physicians India* 2001; *49* : 442-5.
31. Keramet A, Bhambhri R, Chakravarty D, Mithal A. Spinal bone mineral density in healthy urban Asian Indian women presenting for a preventive health check-up. *J Bone Miner Res* 2003; *18* (Suppl 1) : SA083.
32. Alekel DL, Mortillaro E, Hussain EA, West B, Ahmed N, Peterson CT, *et al*. Lifestyle and biologic contributors to proximal femur bone mineral density and hip axis length in two distinct ethnic groups of premenopausal women. *Osteoporosis Int* 1999; *9* : 327-38.
33. Cundy T, Cornish J, Evans MC, Gamble G, Stapleton J, Reid IR. Sources of interracial variation in bone mineral density. *J Bone Miner Res* 1995; *10* : 368-73.
34. Usha G, Krishnaswamy B. Bone mineral density and fracture threshold in South Indian elderly. *J Assoc Physicians India* 2002; *50* : 247-9.

Reprint requests: Dr Ambrish Mithal, Senior Consultant, Department of Endocrinology & Diabetes Indraparastha Apollo Hospital, Sarita Vihar, New Delhi 110 044, India
e-mail: ambrishmithal@rediffmail.com