THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (July–August 2017) 67(4):237–242
DOI 10.1007/s13224-017-0994-3

INVITED REVIEW ARTICLE

Osteoporosis Prevention and Management

Muralidhar V. Pai[1]

Received: 7 April 2017 / Accepted: 8 April 2017 / Published online: 20 April 2017

About the Author

Muralidhar V. Pai is currently working as Professor and Head, Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal, Manipal University. He has been HOD of Obstetrics and Gynaecology, Melaka Manipal Medical College, Melaka, Malaysia. He has been National Corresponding Editor of Indian Journal of Obstetrics and Gynaecology and Chairman of FOGSI Public Awareness Committee. He is the recipient of "Best Teacher Award," six times, at KMC, Manipal. He is the winner of both Junior and Senior "FOGSI Corion Awards" for Best Research and "FOGSI Imaging Science Award." He is the Fellow of Indian College of Obstetrics & Gynecology. He has been awarded several International Travelling Fellowships. He has co-authored two books "Holland & Brews manual of Obstetrics 4th edn (Elsevier)" and "Obstetrics and Gynecology, PMFU 1st edn (Elsevier)." He has over 100 articles in peer-reviewed scientific journals and contributed several chapters in Obstetrics & Gynecology Textbooks. He has been UG and PG Examiner and Guest Speaker at National and International Universities and Conferences during his 30 years of teaching career. Besides his academic accomplishments, he is a singer and painter.

Abstract Osteoporosis, defined by BMD at the hip or lumbar spine that is less than or equal to 2.5 standard deviations below the mean BMD of a young-adult reference population, is the most common bone disease in humans affecting both sexes and all races. It's a silent killer affecting the quality of life due to fractures and postural changes. In osteoporosis there is an imbalance between bone formation and bone resorption in favor of latter. Preventive measures and treatments are available to combat this evil. Counseling is the integral part of prevention as well as treatment of osteoporosis. Preventive strategy includes life style changes, exercise, intake of calcium and vitamin D, avoiding alcohol, smoking and excessive intake of salt. Estrogen therapy/estrogen+progesterone therapy (ET/EPT) is no longer recommended as a first-line therapy for the prevention of osteoporosis. They may be used in the therapy for osteoporosis in women under 60. Diagnosis and classification are made by assessment of BMD using DEXA or ultrasound and laboratory investigations. Management includes estimation of 10-year fracture risk using FRAX, life style and diet modification and pharmacological therapy. The drugs used in osteoporosis may be those that inhibit bone resorption—bisphosphonates, denosumab, calcitonin, SERMs, estrogen and progesterone—or that stimulate bone formation—PTH, Teriparatide. Combination therapies are not

Muralidhar V Pai is currently working as Professor and Head, Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal, Manipal University.

✉ Muralidhar V. Pai
drmvpai@yahoo.com

[1] Kasturba Medical College, Manipal, Karnataka, India

recommended as they do not have proven additional BMD/fracture benefits. No therapy should be indefinite in duration. There are no uniform recommendations to all patients. Duration decisions need to be individualized. While on treatment monitoring should be done with BMD assessment by DEXA/ultrasound and bone turnover markers.

Keywords Osteoporosis · BMD · DEXA · PRAX · Bisphosphonates · Parathyroid hormone

Introduction

Osteoporosis is the most common bone disease in humans [1] affecting both sexes and all races. Its prevalence increases as the population ages. It's a silent killer that attacks the bones from within, right from adulthood and stepping up its offensive postmenopause due to lower levels of estrogen. The natural consequence of osteoporosis is fractures and their complications, most common among them being fracture of the vertebrae (spine), proximal femur (hip) and distal forearm (wrist). Hip fractures are associated with an 8.4–36% excess mortality within 1 year [2]. Quality of life is also affected due to limitation of activity as a consequence of postural changes.

Fortunately, preventive measures and treatments are available to combat this evil. For those already affected by osteoporosis, early diagnosis of bone loss and assessment of fracture risk are crucial in slowing further loss of bone or increasing bone density. Prevention, detection and treatment of osteoporosis are responsibility of every doctor, especially gynecologist. The objective of this article is to address the prevention, risk assessment, diagnosis and treatment of osteoporosis in women, including indications for bone densitometry and fracture risk thresholds for intervention with pharmacologic agents.

Definition

According to the WHO diagnostic classification, osteoporosis is defined by BMD at the hip or lumbar spine that is less than or equal to 2.5 standard deviations below the mean BMD of a young adult reference population.

Counseling

Counseling is the integral part of prevention as well as treatment of osteoporosis. In fact bone health counseling should begin at adolescence as bone mass after the age of 50 is equal to the bone mass achieved by the age of 18–25 minus the subsequent bone loss [3]. We must impress upon the importance of making calcium deposits early in life. Counseling should also involve education regarding the prevention and early detection of osteoporosis and steps to reduce fractures.

Pathophysiology of Osteoporosis

In osteoporosis there is an imbalance between bone formation and bone resorption in favor of latter. This starts during menopausal transition period and intensifies after menopause. Bone loss leads to an increased risk of fracture which in turn is intensified by age-related musculoskeletal imbalances and use of glucocorticoids.

Genetic factors, endocrine status, nutrition, physical activity and general health during growth play pivotal role in the occurrence of osteoporosis [3].

Prevention

Osteoporosis is preventable as well as treatable, but we need to improve the awareness about the disease in general and the risk factors that lead to the problem. Factors associated with an increased risk of osteoporosis and related fractures are as follows:

- Lifestyle factors—alcohol abuse, smoking, excessive intake of salt and vitamin A, poor physical activity, inadequate intake of vitamin D and calcium
- Genetic diseases—cystic fibrosis, Gaucher's disease, glycogen storage disease, osteogenesis imperfecta, Marfan's syndrome, homocystinuria
- Hypogonadal states—Turner's and Klinefelter's syndrome, panhypopituitarism, premature menopause
- Endocrine disorders—Cushing's syndrome, diabetes mellitus, hyperparathyroidism, thyrotoxicosis
- Gastrointestinal disorders—celiac disease, malabsorption, inflammatory bowel disease, primary biliary cirrhosis
- Hematologic disorders—hemophilia, multiple myeloma, sickle cell disease, thalassemia, leukemia and lymphomas
- Neurological and musculoskeletal factors—multiple sclerosis, epilepsy, muscular dystrophy, stroke
- Rheumatologic and autoimmune diseases—rheumatoid arthritis, systemic lupus
- Miscellaneous—HIV/AIDS, weight loss, depression, post-transplant bone disease.
- Medications—anticoagulants, anticonvulsants, glucocorticoids, GnRH agonists, tamoxephen, aromatase inhibitors, methotrexate, lithium, antidepressants.

Knowing these risk factors will help us in investigating the women and taking adequate precautions.

Simple and most important elements of prevention include diet and exercise. Diet is essential in maintaining bone formation as well as density and should contain adequate calories, protein, optimal calcium and vitamin D. RCTs have shown that the combination of supplemental calcium and vitamin D reduces the risk of fracture [4]. Dietary sources of calcium are milk, cottage cheese, yogurt, hard cheese, green vegetables. Smoking and excessive alcohol should be avoided. Exercise should be performed at least 30 min a day, three times a week. One may alternate all three types (isometric, isotonic and stretching) of exercises. Exercises not only improve agility, strength, posture and balance, they may also increase bone density. Estrogen/Estrogen + Progesterone are no longer recommended as a first-line therapy for the prevention of osteoporosis, especially after the age of 60. Before the age of 60, estrogen is considered only if the woman has menopausal symptoms. Progesterone should be added if the woman has uterus.

Daily calcium and vitamin D requirement [5]:

Premenopausal—calcium 1000 mg/day (includes calcium in food and beverages + supplements). It could be calcium carbonate or calcium citrate. Vitamin D 600 IU/day

Postmenopausal—calcium 1200 mg/day, vitamin D 800 IU/day

Those at risk of fracture should avoid falls, avoid/reduce glucocorticoids, heparin and anti-epileptic drugs.

Management of Osteoporosis

Principles

- Thorough history and assessment of risk factors for osteoporosis as well as fractures and falls
- Physical examination and investigations to know the secondary causes
- Diagnosis and classification of osteoporosis after estimating BMD
- Estimation of 10-year fracture risk using FRAX
- Lifestyle and diet modification
- Pharmacological therapy.

Investigations

The first-line investigations include: CBC, serum calcium, serum phosphorus, 25-OH vitamin D, ALP, TSH, 24-h urine calcium, total protein and albumin. Table 1 gives the interpretation of these. The second-line investigations include: FSH, LH, estradiol, prolactin, PTH, rheumatoid factor, 24-h urine-free cortisol, homocysteine. The above investigations help in determining secondary causes of osteoporosis.

Table 1 Interpretation of first-line investigations

Test	Result	Cause
CBC	Anemia	Multiple myeloma
Calcium	Elevated	Hyperparathyroidism (HPT)
	Low	Vitamin D deficiency, malabsorption
Phosphorus	Elevated	Renal failure
	Low	Hyperparathyroidism
25-OH vitamin D	Low	Malabsorption, celiac disease
ALP	Elevated	Vitamin D deficiency, hyperparathyroidism
Creatinine	Elevated	Renal osteodystrophy
TSH	Elevated	Hypothyroidism
	Low	Hyperthyroidism
Urine calcium	Elevated	Multiple myeloma, HPT
	Low	Inadequate intake of vitamin D and calcium
Serum albumin	Low	Nutritional deficiency
Serum protein	M band	Multiple myeloma

Bone turnover markers are not performed as a routine, as they are very expensive and do not add more to the diagnosis and management of osteoporosis. However, they may be performed in a research setup.

Diagnosis

X-ray is not sensitive, but can detect density, trabecular pattern and deformity. Bone mineral density (BMD) either by dual-energy X-ray absorptiometry (DEXA) is the mainstay of diagnosis of osteoporosis. They also help in monitoring the post-treatment recovery. Additional bone densitometry technologies include quantitative computed tomography (QCT) and/or quantitative ultrasound densitometry. Even though results are not equivalent to DEXA, quantitative ultrasound densitometry is often used for community-based screening programs because of the portability of the equipment and it is a good tool to predict fracture risk, bone quality and bone mass.

Based on BMD two types of scoring systems have been evolved:

T score: SD below the average for a young adult at peak bone density

Z score: SD below an average person of the same age

Based on BMD and T score WHO has classified the osteoporosis as shown in Table 2 [6].

Table 2 WHO classification of osteoporosis

Class	T score	Bone density
Normal	+1 to −1	BMD 0–1 SD below the mean
		Only preventive measures
Osteopenia	−1 to −2.4	BMD 1–2.5 SD below the mean
		At risk of developing osteoporosis if not treated
Osteoporosis	−2.5 or less	BMD > 2.5 SD below the mean
		At higher risk of fractures
Severe osteoporosis	−2.5 or less +1/more #	BMD > 2.5 SD below the mean
		At higher risk of fractures

The International Society for Clinical Densitometry (ISCD) recommends that instead of T scores, ethnic or race-adjusted Z scores should be used, with Z scores of −2.0 or lower defined as either "low bone mineral density for chronological age" or "below the expected range for age" and those above −2.0 being within the expected range for age [7].

There is no need to perform BMD measurement as a routine in adolescents and healthy young or premenopausal women; however, it is indicated in women aged more than 65 years and who are at risk of osteoporosis, especially with a history of fracture.

10-Year Probability of a Major Osteoporotic Fracture

WHO has also developed a Fracture Risk Algorithm (FRAX®) to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (defined as clinical vertebral, hip, forearm or proximal humerus fracture), taking into account femoral neck BMD and the clinical risk factors such as age, gender, BMI, prior osteoporotic fracture and intake of glucocorticoid [6]. This is country specific and available online at www.nof.org as well as at www.shef.ac.uk/FRAX. FRAX® is intended for postmenopausal women.

Drugs Used in Osteoporosis

The drugs used in osteoporosis may be categorized as follows:

1. Drugs that inhibit bone resorption—bisphosphonates, denosumab, calcitonin, SERMs, estrogen and progesterone
2. Drugs that stimulate bone formation—PTH, teriparatide
3. Mixed—vitamin D, strontium ranelate.

Bisphosphonates

These are first-line drugs. They slow the breakdown and removal of bone. They are widely used for prevention and treatment. They should be taken first thing in the morning with 8 oz of plain water, and one should wait for half an hour before taking food/other drugs. Other than gastrointestinal disturbances the serious side effects are avascular necrosis or osteonecrosis of the jaw. Bisphosphonates may be Alendronate (oral once weekly), Risedronate (oral once monthly), Ibandronic acid (IV once monthly), Zoledronic acid (IV once yearly).

Denosumab

It is an antibody directed against a factor receptor activator of nuclear factor kappa-B ligand (RANKL) involved in formation of cells that break down bone. It improves BMD and reduces fracture. It is given in the dose of 60 mg s/c once in 6 months. As it is very expensive, it is reserved for intolerant/unresponsive to oral and/or IV bisphosphonates.

Calcitonin

It helps to regulate calcium concentrations. It is not clear if it improves bone. It has analgesic property; hence, it is used as first-line therapy for those who have a sudden, intense (acute) onset of pain due to vertebral fractures. It is administered via injection or nasal spray

SERMs

They provide protection against bone loss but are less effective than bisphosphonates or estrogen. They decrease the risk of breast cancer. Not recommended for premenopausal women and one should avoid them in case the woman has hot flushes, especially raloxifene.

Estrogen Therapy/Estrogen + Progesterone Therapy (ET/EPT)

They reduce hip and vertebral fracture risk by 34%. Estrogen has additional advantage of controlling menopausal symptoms. National Osteoporosis Foundation no longer recommends ET/EPT as a first-line therapy for the prevention of osteoporosis [8]. They may be used in the therapy for osteoporosis in women under 60; however, they are not recommended for treatment in postmenopausal women after 60 years. They may be appropriate for prevention of osteoporosis in premature menopause. WHO study has shown that medroxyprogesterone acetate slightly increases the risk of breast cancer [9]. Estrogen may increase stroke and clots. Safety and efficacy increased if

estrogen is given by transdermal/vaginal route. Human estradiol is better.

Parathyroid Hormone (PTH)

It is the only medication that works by stimulating bone formation. It is effective in prevention and treatment of osteoporosis in postmenopausal women. It is more effective at building spine bone density and reducing spine fracture risk than any other treatment. It's expensive, requires a daily injection and is reserved for patients with severe hip or spine osteoporosis. It should not be given to postmenopausal women with hypercalcemia, bone metastases.

Vitamin D

Vitamin D has double benefit. It increases the BMD and hence decreases the incidence of fracture by 25%. It also increases muscle strength balance and lower extremity function and hence decreases the rate of fall by 25%. However, results using vitamin D in postmenopausal osteoporosis are mixed. It is effective in preventing glucocorticoid-induced and post-transplant-related bone loss. When on calcitriol one should give a low-calcium diet and monitor for hypercalcemia, hypercalciuria and renal insufficiency.

Strontium Ranelate

It is orally active and has two atoms of strontium + ranelic acid. It stimulates osteoblast and has a modest anti-resorptive effect. It has little effect on bone formation.

Management in Special Situations

Premenopausal Women

BMD screening is not routinely recommended for premenopausal women [10]. Screening with BMD is needed for women

- with history of fragility fracture
- with diseases, conditions or medications associated with low bone mass or bone loss
- on therapy for osteoporosis
- in transition and specific risk factor for fracture (e.g., low body weight, prior low-trauma fracture or high-risk medication)

Treatment in premenopausal age group includes: calcium, vitamin D and weight-bearing exercise plus anti-fracture therapies such as bisphosphonates/SERMs/teriparatide (PTHa). ET/EPT is used only in proven deficiency and/or in women with symptoms suggestive of estrogen deficiency.

Postmenopausal Women

Treatment is indicated in postmenopausal women with

- History of hip or vertebral fracture
- Osteoporosis (T score ≤ -2.5)
- Osteopenia (T score -1.0 to -2.5)
- 10-year risk of fracture (hip $\geq 3\%$ others $\geq 20\%$)

Treatment in postmenopausal age group includes:

Bisphosphonates are the first-line therapy in postmenopausal women with osteoporosis or osteopenia. Initial therapy may be with oral bisphosphonates, and the drug of choice is Alendronate or Risedronate.

The second line of therapy is injection denosumab especially for those who are intolerant of/unresponsive to other therapies and those at high risk of fracture or with impaired renal function.

For those who don't tolerate bisphosphonates, SERMs/strontium ranelate may also be tried. For those who do not respond, PTH may be given. ET/EPT is given only in the presence of menopausal symptoms that too under the age of 60. In the presence of severe pain calcitonin may be considered.

Combination therapies are not recommended as they do not have proven additional BMD/fracture benefits.

Other drugs that may be given are vitamin D, vitamin K, folate, vitamin B12, tibolone, androgens, isoflavones, fluoride.

No therapy should be indefinite in duration. There is no uniform recommendation to all patients. Duration decisions need to be individualized. While on treatment monitoring should be done with BMD assessment by DEXA/ultrasound and bone turnover markers.

Emerging Drugs

- Sclerostin inhibitors—sclerostin is produced by osteocytes and inhibits bone formation
- Integrin antagonists—integrins mediate the adhesion of osteoclasts to the bone surface, an important initial step for bone resorption
- Cathepsin K inhibitors—cathepsin K is a protease in osteoclasts and plays a role in osteoclast-mediated bone resorption.

Summary of Recommendations

- Start counseling regarding bone health early in adolescence

- Promote intake of calcium-rich diet and/or supplements (totaling to a minimum 1000 mg per day) as well as vitamin D (800 IU per day)
- Advice to avoid smoking and excessive alcohol
- Stress on the need of regular weight-bearing and muscle-strengthening exercise
- Assess the clinical risk factors for osteoporosis, falls and 10-year probability of fracture using FRAX
- Screen for BMD using DEXA or ultrasound in high-risk premenopausal and postmenopausal women
- Diagnose and classify using WHO classification
- Initiate appropriate pharmacotherapy promptly along with calcium and vitamin D in therapeutic doses and monitor with BMD
- Recommended drugs—bisphosphonates (first-line therapy), denosumab (second-line therapy), PTH (for those who do not respond), calcitonin (for those with pain), ET/EPT (in women with proven deficiency and menopausal symptoms under the age of 60).

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

Ethical approval No procedure was performed while writing this review article. However ethical standards were observed while writing the article as per Institutional and/or National research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Question doesn't arise as its not an original article.

References

1. Office of the Surgeon General (US). Bone health and osteoporosis: a report of the surgeon general. Rockville: Office of the Surgeon General (US); 2004. http://www.ncbi.nlm.nih.gov/books/NBK45513/. Accessed Mar 2014.
2. Abrahamsen B, van Staa T, Ariely R, et al. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633–50.
3. Khosla S, Riggs BL. Pathophysiology of age-related bone loss and osteoporosis. Endocrinol Metab Clin N Am. 2005;34:1015–30.
4. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res. 2004;19(3):370–8.
5. Institute of Medicine (US) committee to review dietary reference intakes for vitamin D and calcium. In: Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary reference intakes for calcium and vitamin D. Washington: National Academies Press (US); 2011. http://www.ncbi.nlm.nih.gov/books/NBK56070/. Accessed Mar 2014.
6. Kanis JA, on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health care level. Technical report. World Health Organization Collaborating Center for Metabolic Bone Diseases. University of Sheffield; 2007.
7. International Society for Clinical Densitometry. 2013 Official positions—adult. http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/. Accessed Feb 2014.
8. Cosman F, de Beur SJ, LeBoff MS, et al. Lindsay clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359–81.
9. Gerardo Heiss MD, Robert Wallace MD, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA. 2008;299(9):1036–45. doi:10.1001/jama.299.9.1036.
10. Schousboe JT, Shepherd JA, Bilezikian JP, et al. Executive summary of the 2013 ISCD position development conference on bone densitometry. JCD. 2013;16(4):455–67.