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Clinical Approach to Patients with Osteoporosis

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Abstract

Osteoporosis is the most common bone disease in humans, acting as a major burden on already burgeoning health care systems. It is a progressive, systemic, skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue, accompanied by a heightened susceptibility to fracture. It is a silent disease until it is complicated by fractures – fractures that occur following minimal trauma or, in some cases, simply as a sequelae of daily activities. However, we can prevent it's occurence with timely diagnosis and optimal treatment. A holistic diagnostic approach is crucial to diagnose this condition and initiate therapy before complications set in. Bone Mineral Density (BMD) testing is a vital component in the diagnosis and management of osteoporosis. It has been shown to correlate with bone strength and is an excellent predictor of future fracture risk. The treatment of osteoporosis encompasses both pharmacological therapy and lifestyle modifications. There are a number of drugs which have been approved by the FDA for the same; however, Bisphosphonates are currently the forerunners in the management of osteoporosis with an unmatched anti fracture efficacy.

Keywords : Osteoporosis, BMD, bisphosphonates.

Introduction

Osteoporosis is the most common bone disease in humans, acting as a major burden on the already burgeoning healthcare systems. It is a progressive, systemic, skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue, accompanied by a heightened susceptibility to fracture[1].

Worldwide, it is estimated that 1 in 3 women above the age of 50 will experience an osteoporotic fracture, as well as 1 in 5 men[1]. In 2013, sources estimate that 50 million people in India were either osteoporotic (T-score lower than 2.5) or had low bone mass (T score between 1.0 and 2.5)[2]. A study in Delhi estimated the prevalence of osteoporosis as 24.6% in men and 42.5% in women, above 50 years of age[3]. Another study by Sharma *et al* has reported a prevalence of osteoprosis of 8.5% at the femoral neck in men[4].

Osteoporosis is a silent disease until it is complicated by fractures – fractures that occur following minimal trauma or, in some cases, simply as a sequel of daily activities. The most common fractures are those of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist). However, we can prevent it's occurence with timely diagnosis and optimal treatment.

What is osteoporosis

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 (T-score). This definition applies only to post-menopausal women and men with age more than 50 years[5].

Certain population groups have been demarcated as atypical yet high risk patients. They are as follows: Premenopausal women, men less than 50 years of age, children. In these groups, the diagnosis of osteoporosis should not be made on the basis of densitometric criteria alone. 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"[6].

Diagnostic assessment

1. History and physical examination – risk assessment

All post-menopausal women and men aged 50 and older should be evaluated for osteoporosis risk in order to determine the need for BMD testing and/or vertebral imaging.

Various risk factors for osteoporosis are as follows:

I. Non-modifiable factors: Age, family history, female gender, etc.

II. Lifestyle related: Smoker, sedentary lifestyle, alcoholic, etc.

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III. Drug related: Glucocorticoids, thyroxine, lithium, etc.[7].

2. Laboratory investigations

There are a variety of plausible differentials associated with low BMD that fall into the domain of secondary osteoporosis, that is, distinct clinical entities which encompass low BMD within their pathological foray and whose treatment will result in its resolution.

Causes of secondary osteoporosis in adults are as follows:

I. Endocrine causes: Diabetes, hyperthyroidism, hyperparathyroidism, etc.

II. Drugs: Proton pump Inhibitors, steroids, SSRI, lithium, etc.

III. Chronic liver disease.

IV. Chronic kidney disease.

V. Malabsorption syndromes: Celiac disease, Crohn's, cystic fibrosis, etc.[7].

Above enlisted causes mandate the use of investigations such as CBC, LFT, KFT, serum calcium, phosphorus, ALP, serum 25 (OH), vitamin D, thyroid function tests, parathyroid hormone, protein electrophoresis, urinary calcium, anti endomysial antibody, etc., to rule-out preventable causes of osteoporosis[7].

3. BMD (bone mineral density)

BMD testing is a vital component in the diagnosis and management of osteoporosis. It has been shown to correlate with bone strength and an excellent predictor of future fracture risk.

T and Z scores in BMD

T-score is bone density compared with what is normally expected in a healthy young adult of same sex. T-score is the number of units – called standard deviations – that bone density is above or below the average. Whereas Z-score is the number of standard deviations above or below what's normally expected for someone of same age, sex, weight, and ethnic or racial origin[8].

The BMD diagnosis of normal, low bone mass (osteopenia), osteoporosis,and severe or established osteoporosis is based on the WHO diagnostic classification (Table I)[8].

Table I: WHO classification of osteoporosis.

Classification	T-score
Normal	T-score -1.0 and above
Osteopenia (low bone mass)	T-score between -1.0 and -2.5
Osteoporosis	T-score at or below -2.5

Box I: Indications for BMD testing

Consider BMD testing in the following individuals:

- Women – age 65 and older, and men – age 70 and older, regardless of clinical risk factors
- Younger post-menopausal women, women in the menopausal transition, and men age 50 to 69 with clinical risk factors for fracture
- Adults who have a fracture at or after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months) associated with low bone mass or bone loss[7].

The World Health Organisation and the International Osteoporosis Foundation recommend that the reference technology for the diagnosis of osteoporosis is dual-energy X-ray absorptiometry (DXA) applied to the femoral neck. The femoral neck is the preferred site because of its higher predictive value for fracture risk[7]. No guidelines have been issued regarding screening intervals or cessation of screening due to insufficient data. A minimum of 2 years gap must be there between screenings to reliably measure BMD change because of limitations in test precision. For normal BMD at baseline, clinicians may wait up to 15 years before repeat screening. Osteopenia at baseline can be screened every 5 years[10].

4. Vertebral imaging

A vertebral fracture is consistent with a diagnosis of osteoporosis, even in the absence of a bone density diagnosis, and is an indication for pharmacologic treatment with osteoporosis medication to reduce subsequent fracture risk[11].

Box II: Indications for vertebral imaging.

Consider vertebral imaging tests for the following individuals:[A]

- All women aged 70 years and older and all men aged 80 years and older if BMD T-score at the spine, total hip, or femoral neck is ≤ – 1.0
- Women aged 65 to 69 years and men aged 70 to 79 years if BMD T-score at the spine, total hip, or femoral neck is ≤ – 1.5
- Post-menopausal women and men aged 50 years and older with specific risk factors:
  - Low-trauma fracture during adulthood (age 50 years and older)
  - Historical height loss of 1.5 in. or more (4 cm)[B]
  - Prospective height loss of 0.8 in. or more (2 cm)[C]
  1. – Recent or ongoing long-term glucocorticooid treatment

A If bone density testing is not available, vertebral imaging may be considered based on age alone

B Current height compared to peak height during young adulthood

C Cumulative height loss measured during interval medical assessment[7].

5. FRAX

FRAX was developed 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[12].

6. Bone biomarkers

There are two types of bone biomarkers.

***Bone formation biomarkers*:** Alkaline phosphatase (ALP), Bone-specific alkaline phosphatase (BALP), Osteocalcin (OC), Procollagen type 1 N-terminal propeptide (P1NP), Procollagen type 1 C-terminal propeptide (P1CP), etc.[13].

***Bone resorption biomarkers*:** Hydroxyproline (HYP), Hydroxylysine (HYL), Deoxypyridinoline (DPD), Pyridinoline (PYD), Bone sialoprotein (BSP), Osteopontin (OP), Tartrate-resistant acid phosphatase 5b (TRAP 5b), Carboxy-terminal crosslinked telopeptide of type 1 collagen (CTX-1), Amino-terminal crosslinked telopeptide of type 1 collagen (NTX-1), Cathepsin K (CTSK)[13].

Uses of bone biomarkers:

1. Predict risk of fracture independent of bone density in untreated patients.
2. Predict rapidity of bone loss in untreated patients.
3. Predict extent of fracture risk reduction when repeated after 3 - 6 months of treatment with FDA-approved therapies.
4. Predict magnitude of BMD increases with FDA-approved therapies.
5. Help determine adequacy of patient compliance and persistence with osteoporosis therapy.
6. Help determine duration of "drug holiday" and when and if medication should be restarted[13].

Given limitations such as biologic variability and difference in assays, these markers are not yet included in algorithms that calculate fracture risk, but they are being used to monitor osteoporosis treatment[13].

Among these bone biomarkers, P1NP has shown the greatest potential as a sensitive and stable bone biomarker for the early detection of osteoporosis[13].

Treatment

1. Whom to treat

- In patients with hip or vertebral (clinical or asymptomatic) fractures.
- In individuals with T-scores ≤ – 2.5 at the femoral neck, total hip, or lumbar spine by DXA.
- In post-menopausal women and men aged 50 years and older with low bone mass (T-score between – 1.0 and – 2.5, osteopenia) at the femoral neck, total hip, or lumbar spine by DXA and a 10-year hip fracture probability ≥ 3 % or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the WHO absolute fracture risk model[7].

2. Pharmacological therapy

Current FDA-approved pharmacologic options for osteoporosis are:

1. Bisphosphonates (alendronate, Ibandronate, risedronate, and zoledronic acid).
2. Receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor (denosumab).
3. Parathyroid hormone 1 - 34 (teriparatide).
4. Calcitonin,
5. Oestrogen agonist/antagonist (raloxifene), oestrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated oestrogens/bazedoxifene)[7].

Bisphosphonates (BPs)

They are recommended as the first-line medications for treatment of osteoporosis. Their effects on bone cells are most notable through inactivating osteoclastic bone resorption and accelerating apoptosis of osteoclasts. BPs can increase BMD, and decrease fracture risk[7]. Oesophageal irritation and erosion can occur with oral bisphosphonate therapy, particularly in patients with known gastro-oesophageal reflux disease or oesophageal stricture. Strict maintenance of an upright posture for 30 to 60 minutes after ingestion with a full glass of water, depending on the oral bisphosphonate, and the use of weekly rather than daily preparations are both likely to limit the risk of adverse effects. For patients unable to tolerate oral bisphosphonates, IV preparations are now FDA approved and not associated with gastro-oesophageal irritation[7].

Box III: Dosage of bisphosphonates.

- Alendronate: 10 mg daily or 70 mg once a week.
- Risedronate: 5 mg daily or 35 mg once a week.
- Ibandronate: 150 mg once a month or 3 mg IV every 3 months.
- Zoledronic acid: 5 mg IV once a year.

Side-effects

Side-effects are similar for all oral bisphosphonate medications and include gastrointestinal problems such as difficulty in swallowing and inflammation of the oesophagus and stomach. There have been rare reports of osteonecrosis of the jaw (ONJ) and low trauma atypical femur fracture with long-term use of bisphosphonates for osteoporosis, though these side-effects are much more common with long-term use of bisphosphonates[14].

Denosumab

Approved by the FDA for the treatment of osteoporosis in post-menopausal women at high risk of fracture.

Dose: Subcutaneous injection of 60 mg once every 6 months[15].

Teriparatide

Teriparatide is approved by the FDA for the treatment of osteoporosis in post-menopausal women and men at high risk for fracture. It is also approved for treatment in men and women at high-risk of fracture with osteoporosis associated with sustained systemic glucocorticoid therapy.

Dose: Subcutaneous injection in a dose of 20 µg/day. The duration of treatment is limited to 24 months[16].

Calcitonin

Salmon calcitonin is FDA-approved for the treatment of osteoporosis in women who are at least 5 years post-menopausal when alternative treatments are not suitable.

Dose: Two hundred international units delivered as a single daily intranasal spray. Subcutaneous administration by injection also is available.

Oestrogen therapy

Once considered the "treatment of choice" for post-menopausal osteoporosis, oestrogen was never specifically approved for this use. It is approved by the FDA for prevention of post-menopausal osteoporosis with the added caveat, "when prescribing solely for the prevention of post-menopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-oestrogen medications are not considered to be appropriate".

Hormone therapy is no longer considered first-line therapy for osteoporosis.

FDA recommends alternative treatment options if oestrogen is being considered solely for osteoporosis treatment[18].

To summarise, bisphosphonates are currently the forerunners in the management of osteoporosis with an unmatched anti-fracture efficacy as depicted below (Table II).

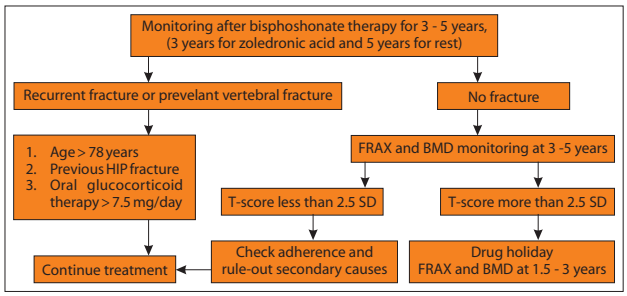
Table II: Anti-fracture efficacy of approved treatments.

Drugs	Vertebral Fracture	Non vertebral fracture	HIP fracture
Alendronate	+	+	+
Ibandronate	+	+	Not adequately evaluated
Risedronate	+	+	+
Zoledronic Acid	+	+	+
Denosumab	+	+	+
Teriparatide	+	+	Not adequately evaluated
Calcitonin	+	Not adequately evaluated	Not adequately evaluated
HRT	+	+	+
Raloxifene	+	Not adequately evaluated	Not adequately evaluated

HRT: Hormone replacement therapy

Monitoring and follow-up of patients

There are several published guidelines for monitoring the response to osteoporosis therapy; all recommend follow-up BMD (DXA) testing. However, there is no consensus on the optimal frequency of monitoring and preferred site to monitor. The use of biochemical markers of bone turnover for monitoring response to therapy has not been addressed in current guidelines, and there are no prospective trials to define the most optimal approach for incorporating markers into monitoring strategies[19] (Alogrithm I).



Algorithm I: Approach to monitoring after bisphosphonate therapy.

Glucocorticoid-induced osteoporosis

A working group from the International Osteoporosis Foundation and the European Society of Calcified Tissues published a framework for the development of national

guidelines for the management of glucocorticoid-induced osteoporosis in men and women aged 18 years or over in whom continuous oral glucocorticoid therapy was considered for 3 months or longer. The low cost of generic formulations of alendronate and risedronate make them first-line options in the majority of cases. In individuals who are intolerant of these agents, or in whom they are contraindicated, zoledronic acid, denosumab or teriparatide are appropriate options[20].

Conclusion

Osteoporosis, despite being a very common bone disease, is seldom diagnosed before being complicated by a fracture. However, a fracture does not sound a gong of clinical decline. Awareness of the disease energises intensive efforts to treat it. Thus, prevention, detection, and treatment of osteoporosis should be a mandate of primary care providers.

References

1. Kanis JA, Johnell O, Oden A *et al.* Long term risk of osteoporotic fracture in Malmö. *Osteoporos Int* 2000; 11: 669-74.
2. Mithal A, Kaur P. Osteoporosis in Asia: A call to action. *Curr Osteoporos Rep* 2012; 10: 245-7.
3. Thulkar J, Singh S. Overview of research studies on osteoporosis inmenopausal women since the last decade. *J Midlife Health* 2015; 6: 104-7.
4. Sharma B, Prakash V, Agrawal N *et al*. Prevalence of maleosteoporosis in India. *Ind J Endocrinol Metab* 2012; 16: S5-19.
5. World Health Organisation. Assessment of Fracture Risk and Its Application to Screening for Post-menopausal Osteoporosis. Report of a WHO Study Group. Geneva: World Health Organisation; 1994.
6. International Society for Clinical Densitometry. 2013 Official Positions – Adult. http://www.iscd.org/official-positions/2013-iscd-official-positions-adult. Accessed Feb 2014.
7. Cosman F, De Beur SJ, Le Boff MS *et al*. Clinician's guide to prevention and treatment of osteoporosis. *Osteopor Int* 2014; 25 (10): 2359-81.
8. Kanis JA, Melton LJ 3rd, Christiansen C *et al*. The diagnosis of osteoporosis. *J Bone Miner Res* 1994; 9 (8): 1137-41.
9. Compston J, Cooper A, Cooper C *et al.* UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2017; 12 (1): 43.
10. Kanis JA, on behalf of the WHO Scientific Group. Assessment of osteoporosis at the primary healthcare level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK, Sheffield 2008.
11. Melton LJ, Chrischilles EA, Cooper C *et al*. How many women have osteoporosis? *J Bone Miner Res* 2005; 20 (5): 886-92.
12. Kanis JA, on behalf of the World Health Organisation Scientific Group (2007) Assessment of osteoporosis at the primary health carelevel. Technical Report. World Health Organisation Collaborating Center for Metabolic Bone Diseases. University of Sheffield, UK.
13. Burch J, Rice S, Yang H *et al*. Systematic review of the use of boneturnover markers for monitoring the response to osteoporosis treatment:the secondary prevention of fractures, and primary prevention of fractures in high-risk groups. *Health Technol Assess (Winchester, England)* 2014; 18 (11): 1-206.
14. Khosla S, Burr D, Cauley J, American Society for Bone and Mineral Research *et al.* Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007; 22 (10): 1470-91.
15. Cummings SR, San Martin J, McClung MR *et al.* Denosumab for prevention of fractures in post-menopausal women with osteoporosis. *N Engl J Med* 2009; 361 (8): 756-65, Erratum in: *N Engl J Med* 2009; 361 (19): 1914.
16. Neer RM, Arnaud CD, Zanchetta JR *et al*. Effect of parathyroidhormone (1 - 34) on fractures and bone mineral density in post-menopausal women with osteoporosis. *N Engl J Med* 2001; 344 (19): 1434-41.
17. Chesnut CH 3rd, Silverman S, Andriano K *et al.* A randomised trial of nasal spray salmon calcitonin in post-menopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 2000; 109 (4): 267-76.
18. Camacho PM, Petak SM, Binkley N *et al*. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice guidelines for the diagnosis and treatment of post-menopausal osteoporosis – 2016. *Endocrine Practice* 2016; 22 (s4): 1-42.
19. Wolfhagen FH, van Buuren HR, den Ouden JW *et al*. Cyclical etidronate in the prevention of bone loss in corticosteroid-treated primary biliary cirrhosis. A prospective, controlled pilot study. *J Hepatol* 1997; 26: 325-30.
20. Lekamwasam S, Adachi JD, Agnusdei D *et al.* A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. *Osteoporos Int* 2012; 23: 2257-76.