Review Article

Osteoporosis: A preventable silent killer but not well addressed

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Abstract

Osteoporosis is characterized by low bone density, micro-architectural deterioration of the bone tissue, enhanced bone fragility and increasing susceptibility to fracture. Osteoporosis is an important public health problem leading to an increased risk of developing spontaneous and traumatic fractures. It is a silent disease until it is complicated by fractures that can occur following minimal trauma. These fractures are common and place an enormous medical and personal burden on individuals during aging and a major economic toll on the nation. To reduce the burden high-risk patients must be identified, evaluated for factors contributing to skeletal fragility, and should be treated to reduce fracture risk. Osteoporosis is a preventable disease and can be diagnosed and treated before any fracture occurs. Importantly, even after the first fracture has occurred, there are effective treatments to decrease the risk of further fractures. Both Pharmacologic and non- pharmacological interventions can reduce the risk for fracture in appropriately selected patients, with a generally favorable safety profile.

Key Words: *Osteoporosis, fracture*

Introduction

Osteoporosis is the one of the most common bone disease & affects millions of people worldwide. It is defined as low bone density with micro architectural deterioration of bone tissue leading to enhanced bone fragility & increased fracture risk. Osteoporosis is often asymptomatic for many years until the end-organ complications (fractures) occur. These fractures and their consequences, which include pain, disability, deformity, and sometimes premature death, are recognized clinical sequelae of osteoporosis. Normally in adults resorbed bone is replaced by an equal amount of new bone tissue. Thus the mass of skeleton remains constant after peak bone mass is achieved in childhood. After 40 years however the resorption and formation process become imbalanced and resorption exceeds formation. Excessive bone loss is due to an increase in osteoclastic activity or as decrease in osteoblastic activity. The prevalence of osteoporosis increases with age, reflecting the fact that bone density declines with age, especially in women. Chronic diseases that increase the risk of falling or frailty including dementia Parkinson's disease and multiple sclerosis also increase fracture risk. Osteoporotic bone is more likely to fracture than normal bone at any level of trauma and a fracture in a person over 50 should trigger evaluation for osteoporosis. This often does not occur because post fracture care is not always well coordinated. Fractures are themselves also risk factors for future fractures. Vertebral fractures increase the risk of other vertebral fractures as well as fractures of the peripheral skeleton such as the hip and wrist. Wrist fractures also increase the risk of vertebral and hip fractures. The risk for subsequent fractures is particularly high in the first several years after the first fracture and the risk wanes considerably thereafter. Consequently among individuals over age 50, any fracture should be considered as potentially related to osteoporosis regardless of the circumstances of the fracture.[1-4]

Epidemiology

Bone mass is a major determinant of fracture risk. For every 10% decline in bone mass, there is an approximate doubling of fracture risk in the population. Fractures related to osteoporosis are estimated to affect around 30% of women and 12% of men in developed countries, and are a major public health problem. In the UK alone, fractures are sustained by over 250 000 individuals annually, with treatment costs of about £1.75 billion. In the United States and Europe, osteoporosis-related fractures are more common among women than men, presumably due to a lower peak bone mass as well as postmenopausl bone loss in women. However this sex difference in bone density and age-related increase in hip fractures is not as apparent in some other cultures possibly due to genetics, physical activity level, or diet. In the United States, as many as 9 million adults have osteoporosis (T-score <-2.5 in either spine or hip) and an additional 48 million individuals have bone mass levels that put them at increased risk of developing osteoporosis (e.g., bone mass T score <-1.0).

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There are about 550, 000 vertebral crush fractures, 400,000 wrist fractures and 135000 pelvic fractures per year in the United States which currently costing a total of about s 15 billion annually. Only a fraction (estimated to be one-third) of them are recognized clinically because many are relatively asymptomatic and are identified incidentally during radiography for other purposes. Vertebral fractures rarely require hospitalization but are associated with long-term morbidity and a slight increase in mortality rates, primarily related to pulmonary disease. The probability that a 50-year-old white individual will have a hip fracture during his or her lifetime is 14% for women and 5% for men; the risk for African Americans is lower and the risk for Asians is roughly equal to that for whites.[1-4]

Pathophysiology

Normally function of osteoclast is bone resorption and osteoblast is osteoid formation &mineralization. After the age of 40 yrs bone resorption is more than formation i.e. increase in osteoclastic activity and/or decrease in osteoblastic activity. If osteoclast penetrate In trabecular bone they leave no template for new bone formation causing rapid bone loss. In cortical bone it causes activation of remodeling and ultimately more porous bone is formed. In women there is an accelerated phase of bone loss after the menopause due to oestrogen deficiency, which causes uncoupling of bone resorption and bone formation, such that the amount of bone removed by osteoclasts exceeds the rate of new bone formation by osteoblasts. Age-related bone loss is a distinct process that accounts for the gradual bone loss that occurs with advancing age in both genders. Bone resorption is not particularly increased but bone formation is reduced and fails to keep pace with bone resorption.[1,2]

Peak bone mass and bone loss are regulated by both genetic and environmental factor, Polymorphisms have been identified in several genes that contribute to the pathogenesis of osteoporosis and many of these are in the RANKL (Receptor activator of nuclear factor kappa-B ligand) and Wnt signalling pathways, which play a critical role in regulating bone turnover. Environmental factors, such as exercise and calcium intake during growth and adolescence, are important in maximizing peak bone mass and in regulating rates of post-menopausal bone loss. Smoking has a detrimental effect on bone mineral density (BMD) and is associated with an increased fracture risk, partly because female smokers have an earlier menopause than non-smokers. Heavy alcohol intake is a recognized cause of osteoporosis and fractures, but moderate intake does not substantially alter risk. The most common causes of male osteoporosis are hypogonadism, corticosteroid use and alcoholism and smoking. A important cause of osteoporosis in both sexes is corticosteroid. Although there is no 'safe' dose of corticosteroid, the risk increases when the dose of prednisolone exceeds 7.5 mg daily and is continued for more than 3 months.[1-4] (Figure-1)

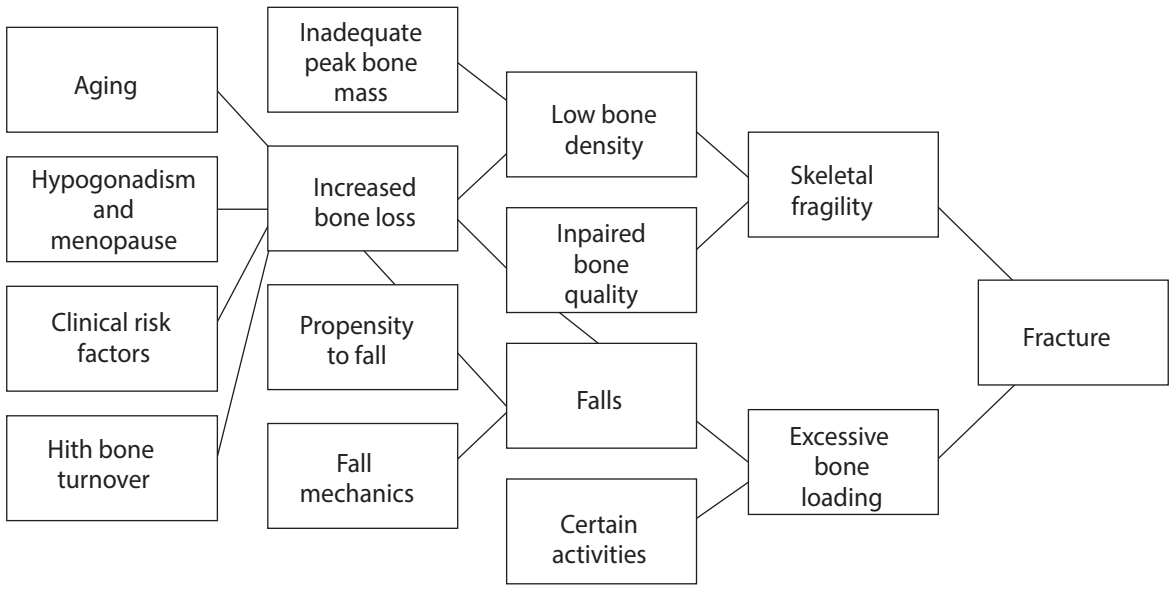

Figure-1 : *Pathogenesis of Osteoporosis-Related Fractures*[1]

Table – I: Clinical risk factors for osteoporosis and low-trauma fracture[3]

- Advanced age
- Female sex
- Estrogen deficiency (any cause after puberty)
- History of fracture as an adult
- History of fragility fracture in first degree relative
- History of glucocorticoid use for more than 3 months
- Current cigarette smoking
- Low body weight (<127 lbs)
- Poor health/frailty
- White race, Asian race
- Low calcium intake
- Alcoholism
- Inadequate physical activity
- Dementia; cognitive impairment, Recurrent falls
- Impaired neuromuscular function and other parameters of immobility
- Impaired eyesight despite optimal correction
- Residence in a nursing home
- Long-term heparin therapy, Anticonvulsant therapy
- Aromatase-inhibitor therapy,
- Androgen-deprivation therapy

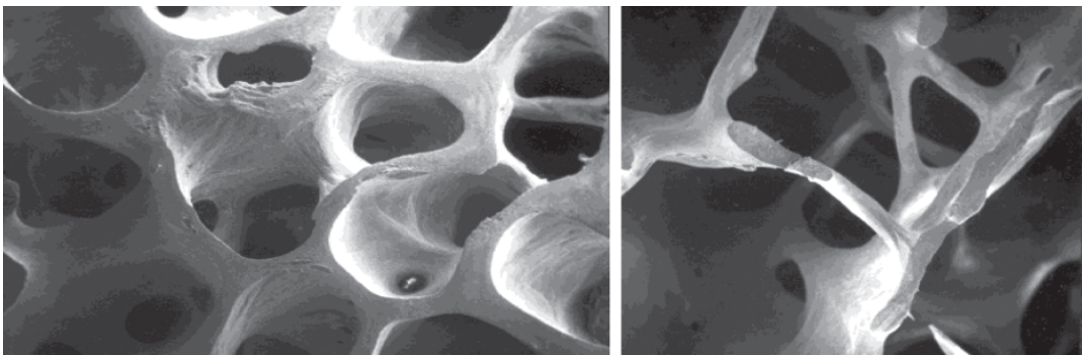

Figure 2: *Micrographs of Normal vs Osteoporotic Bone*

Classification of osteoporosis[2-3]

Osteoporosis may be primary or secondary. Primary osteoporosis may be postmenopausal (Type I) caused by lack of estrogen, which causes uncoupling of resorption and bone formation, such that the amount of bone removed by osteoclasts exceeds the rate of new bone formation by osteoblasts. Primary osteoporosis may also be age-associated (Type II) where bone resorption is not particularly increased but bone formation is reduced and fails to keep pace with bone resorption.

Table-II: Secondary causes of osteoporosis and osteoporotic fractures[1]

Endocrine disease
- Hypogonadism
- Hyperthyroidism
- Hyperparathyroidism
- Cushing's syndrome

Inflammatory disease
- Inflammatory bowel disease
- Ankylosingspondylitis
- Rheumatoid Arthritis

Drugs
- Corticosteroids
- Gonadotrophin-releasing hormone (GnRH) agonists
- Aromatase inhibitors
- Thyroxine over-replacement
- Thiazolidinediones
- Sedatives
- Anticonvulsants
- Alcohol intake >3 U/day
- Heparin

Gastrointestinal disease
- Malabsorption
- Chronic liver disease

Lung disease
- Chronic obstructive pulmonary disease
- Cystic fibrosis

Miscellaneous
- Myeloma
- Homocystinuria
- Anorexia nervosa
- Highly trained athletes
- HIV infection
- Gaucher's disease
- Systemic mastocytosis
- Immobilisation
- Body mass index <18
- Heavy smokers
- Autoantibodies to osteoprotegerin (OPG)

Clinical Presentation

Most patients are asymptomatic and diagnosis is made only after a fracture. Common sites of fracture s are spine, hip, and wrist. Common clinical presentations include increasing dorsal kyphosis, low trauma fracture, loss of height and back pain. Ultimately it causes chronic pain, height loss, kyphosis, decreased self-esteem, Restrictive lung diseases, Constipation, abdominal pain, depression etc.[1-4] Consequences of hip fractures are 5-20% mortalities within one year, 10% severely impaired mobility after 12 months, 50% don't regain previous mobility.[5]

Potentially Helpful Findings on Physical Examination for Osteoporosis [3]

- Loss of height may be associated with vertebral fracture
- Low body weight is an independent risk factor for fracture
- Weight loss may be due to hyperthyroidism or malnutrition
- Fast heart rate may be due to hyperthyroidism or anemia
- Fast respiratory rate may be due to asthma
- Kyphosis may be the result of vertebral fractures or upper back muscle weakness, Poor gait, muscle strength, balance may increase the risk for falls and fractures, Paralysis or immobility may result in bone loss, increased risk for falls, or both joint laxity could be due to the Marfan syndrome, osteogenesis imperfecta, or the Ehlers-Danlos syndrome
- Inflammatory arthritis is associated with osteoporosis and the use of glucocorticoids
- Osteoarthritis or lower limb injury may result in decreased load-bearing and bone loss
- Blue sclera, poor tooth development, hearing loss, and fracture deformities are associated with osteogenesis imperfecta
- Poor dental hygiene is a risk factor for osteonecrosis of the jaw with bisphosphonate therapy
- Thyromegaly, thyroid nodules, and proptosis suggest hyperthyroidism
- Urticaria pigmentosa suggests systemic mastocytosis
- Kyphosis or shortened distance between lowest ribs and iliac crest suggests vertebral fractures
- Abdominal tenderness may be due to inflammatory bowel disease
- Stretch marks, buffalo hump, and bruising suggest glucocorticoid excess
- Signs of venous thrombosis suggest that treatment with estrogen or raloxifene maybe contraindicated
- Small testicles in men suggest hypogonadism

Osteoporosis Assessment

Investigations[1-6]

- DEXA (the pivotal investigation. Is DEXA at the lumbar spine, hip and wrist)
- X-ray (Lumbosacral spine, femoral neck, wrist etc.)
- FRAX
- bone resorption [C-telopeptide (CTX)] marker

Table-III : Laboratory Evaluation for Secondary Causes of Osteoporosis[3]

Essential tests	**Comments/Disorder Detected**
Complete blood count	Cancer
Serum calcium	High in hyperparathyroidism
Serum phosphorus	Low with osteomalacia
Serum creatinine	High with chronic kidney disease
Serum thyroid-stimulating hormone	Low in hyperthyroidism
Serum liver enzymes	High with chronic liver disease
Serum alkaline phosphatase	High with chronic liver disease and Pagets disease of bone and low with hypophosphatasia
Serum total/free testosterone In men	Hypogonadism
24-hour urinary calcium	Low (< 50-100 mg/24 h) with calcium malabsorption, High(>250mg/24h in women or >300 > mg/24h in men) With excessive calcium absorption or renal calcium leak
Optional tests according to clinical circumstance	
Serum 25-hydroxyvitamin D	Vitamin D deficiency/insufficiency
Serum parathyroid hormone in patients with high serum calcium	Hyperparathyroidism
Serum/urine protein electrophoresis, Kappa/lambdalight chain	Multiple myeloma in elderly patients
Serum tryptase	Systemic mastocytosis
Serum celiac antibodies (antigliadin, endomysial, tissue transglutaminase) when malabsorption is suspected	celiac disease

Indications for Bone Mineral Density Testing: [1-3]

- Low trauma fracture age >50 years
- Clinical features of osteoporosis (height loss, kyphosis)
- Osteopenia on plain X-ray
- Corticosteroid therapy (>7.5 mg prednisolone daily for3 months)
- Family history of hip fracture
- Low body weight (BMI <18)
- Early menopause (<45 yrs)
- Diseases associated with osteoporosis
- Increased fracture risk on risk factor analysis (FRAX or Q Fracture)
- Assessing response of osteoporosis to treatment

FRAX Tool

The World Health Organization (WHO) has developed a freely available, computer-based fracture risk assessment tool, FRAX that can be used with or without BMD, to estimate the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, forearm) in untreated men and women between the ages of 40 and 90.[6]

Table-IV : FRAX Tool

Clinical items used by the FRAX tool to estimate 10-year risk for major osteoporotic fracture (hip, clinical spine, proximal humerus, distal forearm) and hip fracture:

- Age
- Sex
- Height
- Weight
- Ethnicity (for US calculator only:
- caucasian, black, Hispanic, or Asian)
- Optional item: femoral neck bone
- mineral density (g/cm2)[6]

Yes/no responses to each of the following:

- Previous fracture
- Parent with hip fracture
- Current smoking
- Glucocorticoid use
- Rheumatoid arthritis
- Secondary osteoporosis
- Three or more units of alcohol per day[6]

Table-V : Classification of Bone Mineral Density

Classification of Bone Mineral Density by Dual-Energy X-Ray Absorptiometry [1-4]

- **Normal**: T score above –1
- **Osteopenia:** T score between –1 and –2.5
- **Osteoporosis**: T score at or below –2.5
- **Severe osteoporosis**: T score –2.5 or lower in the presence of 1 or more fractures

T scores vs. Z scores

- **T score** – number of SDs a patient's BMD deviates from a reference population of normal young adults
- **Z score –** number of SDs a patient's BMD deviates from a reference population of subjects of the same age and sex
- **Z scores** indicate whether the BMD result is expected for the patient's age. If it is much less than expected, suspect a secondary cause of osteoporosis (use –2 as a cut off)

In premenopausal women and men under age 50—do not apply the WHO diagnostic criteria

- Z-scores, not T-scores, are preferred
- Z-score of –2.0 or lower is defined as "below the expected range for age"
- Z-score above –2.0 is "within the expected range for age"

In children (males and females less than age 20) - do not apply the WHO diagnostic criteria

- Use Z-scores, not T-scores
- If the Z-score is below –2.0, use such terminology as "low bone density for chronological age" or "below the expected range for age"[6]

Prevention and Treatment

Lifestyle measures are recommended for prevention[1-3, 6]

- Regular physical activity and good nutrition
- Adequate intake of calcium and vitamin D
- Avoidance of smoking and
- Moderate alcohol consumption should be recommended
- Exposure to medications known to have harmful skeletal effects (e.g., glucocorticoids, aromatase inhibitors, androgen-deprivation therapy, and anticonvulsants) should be minimized or avoided.
- For frail, elderly patients, the importance of fall prevention by means including modifying the home

environment; leg-strengthening exercises; balance training; and avoiding drugs that may cause sedation, hypotension, or dizziness should be emphasize.

Treatment goal is to prevent fractures and skeletal deformity, increasing or stabilize or bone mass, relieving symptoms of fractures and maximize physical function.

Who should be treated [1-4]

Postmenopausal women and men age ≥ 50 presenting with:

- A hip or vertebral fracture
- T-score < -2.5 at femoral neck, total hip or spine and secondary causes with high risk factors.
- Other prior fractures &T between -1.0 and -2.5 at femoral neck, total hip, or spine
- Low BMD T- between -1.0 and -2.5 at the femoral neck, total hip, or spine and 10-yr probability of hip fracture ≥3% or a 10-yr probability of any major osteoporosis related fracture ≥ 20%

Bisphosphonate: Bisphosphonates inhibit bone resorption by binding to hydroxyapatite crystals on the bone surface. When osteoclasts attempt to resorb bone that contains bisphosphonate, the drug is released within the cell, where it inhibits key signaling pathways that are essential for osteoclast function.[1-4]

Alendronate : It reduces risk of vertebral fractures by 40% and non-vertebral fractures by about 25% in postmenopausal women with osteoporosis**.** [1-3,7-10]

Dose-For prevention (5 mg daily and 35 mg weekly) -For treatment (10 mg daily and 70 mg weekly) [1-3,7-10]

Ibandronate: Ibandronate is sometimes used but the evidence for prevention of non-vertebral fractures is less robust. Reduces the incidence of spine fracture by about 50% over 3 years. [1-3, 11-12]

Risedronate: Approved for prevention and treatment of postmenopausal, male and Glucocorticoid induced osteoporosis. Reduces incidence of spine fracture by 41-49% & non-spine fracture by 36% over 3 years with a prior spine fracture. [1-3, 13-14] **Dose** -5 mg daily, -35 mg weekly [1-3, 13-14]

Zoledronate: Zoledronic acid is effective in the treatment of post-menopausal osteoporosis, corticosteroid-induced osteoporosis and osteoporosis in men. It is especially useful for secondary prevention of fractures in elderly patients with hip fracture and reduces mortality in this group, being the only treatment that has been shown to modify this. It reduces incidence of spine fracture by 75%, hip fracture by 41%, and non-vertebral fracture by 25% over 3 years.[1-3, 15-16]

Dose-5 mg by intravenous infusion once yearly [1-3, 15-16]

Adverse effects of Bisphosphonates[1]

Common

- Upper gastrointestinal intolerance (oral)
- Acute phase response (intravenous)

Less common

- Atrial fibrillation (intravenous zoledronic acid)
- Renal impairment (intravenous zoledronic acid)
- Atypical subtrochanteric fractures

Rare

- Uveitis
- Osteonecrosis

Table-VI: Pharmacological treatment options for Osteoporosis [1-5, 7-23]

Drug	Post Menopausal OP		Steroid OP		Male OP
	Prevention	Treatment	Prevention	Treatment	
Alendronate	✓	✓		✓	✓
Risedronate	✓	✓	✓	✓	✓
Ibandronate	✓	✓			
Zoledronate	✓	✓	✓	✓	✓
Raloxifene	✓	✓			
Estrogen	✓				
Calcitonin		✓?			
Denosumab		✓		?	
Teriparatide		✓		✓	✓

Use of Bisphosphonates in renal impairment / Chronic Kidney Disease (CKD)[1-5]

CKD Stages 1-3

Patients with CKD stages 1-3 and low T-scores or low trauma fractures, most likely have osteoporosis. Bisphosphonates can be used safely.

CKD Stages 4-5

Bisphosphonates are not recommended for patients with an estimated GFR < 30 ml/min

Calcium and Vitamin D

Calcium and vitamin D have limited efficacy in the prevention of osteoporotic fractures when given in isolation but are widely used as an adjunct to other treatments, most often as combination preparations containing500 mg calcium and 800-1200 U vitamin D3. They are of greatest value in preventing fragility fractures in elderly or institutionalized patients who are at high risk of calcium and vitamin D deficiency. Chief dietary sources of vitamin D include vitamin D-fortified milk, cereals , egg yolks, salt-water fish, and liver .It Should not be used as the first line treatment .[1-3,17]

Estrogen/Hormone Therapy

For prevention of osteoporosis, relief of vasomotor symptoms and vulvo-vaginal atrophy

Decrease hip and vertebral fractures in postmenopausal women.

Adverse effects (increased risk of stroke, cognitive impairment, DVT and cardiovascular diseases) offset benefits

No longer considered as first line therapy [1-2,18]

Raloxifene: It results in a modest increase in BMD (2%) and a 40% reduction in vertebral fractures, but does not influence the risk of non-vertebral fracture and can provoke muscle cramps and worsen hot flushes but reduces the risk of breast cancer. Reduction of hip and other non-vertebral fracture not demonstrated.[1-3, 19-20]

Calcitonin: Calcitonin is an osteoclast inhibitor that has weak anti fracture efficacy but is no longer used in the treatment of osteoporosis because of concerns about an increased risk of cancer with long-term use.[1-3, 21]

Teriparatide: Teriparatide increases BMD by 10% or more in osteoporotic subjects and reduces risk of vertebral fractures by about 65% and non-vertebral fractures by 50%.It is also effective in corticosteroid-induced osteoporosis and appears superior to alendronate in terms of BMD gain and vertebral fracture reduction. It is also effective in male osteoporosis.[1-3, 22]

Strontium ranelate: Strontium ranelate reduces vertebral fracture risk by about 50% after 3 years and non-vertebral fracture risk by 12%. It has a weak inhibitory effect on bone resorption, stimulates biochemical markers of bone formation and is incorporated within hydroxyapatite crystals in place of calcium.[1]

Denosumab: Denosumab is a monoclonal antibody that neutralizes the effects of RANKL. It is administered by subcutaneous injection every 6 months in the treatment of osteoporosis. It is a powerful inhibitor of bone resorption and reduces the risk of hip fractures by 40%, vertebral fractures by 70% and other non-vertebral fractures by 20%.[1-3, 23]

Management of Vertebral Fractures[1]

Conservative:	Oral pain management Physical therapy
Surgical:	Kyphoplasty Vertebroplasty

Evaluating Treatment Efficacy

- Serial BMD measurements by DEXA can be used to monitor for response to therapy. It is appropriate to measure BMD 12 to 24 months after initiating or changing therapy and periodically thereafter.
- An increase or stability in BMD is considered an acceptable response to therapy
- Ensure compliance
- A significant loss of BMD usually represents non-response or a suboptimum response to therapy, suggesting the need for reevaluation of treatment and evaluation for secondary causes of osteoporosis and considered for change in therapy.

Measurement of bone resorption (C-telopeptide [CTX] is the preferred marker) before initiating therapy and 3-6 months after starting therapy provides an earlier estimate of patient response than does bone densitometry .A decline in resorptive markers can be ascertained after treatment with potent antiresorptive agents such as bisphosphonates, denosumab, or standard-dose estrogen; this effect is less marked after treatment with weaker agents such as raloxifene or intranasal calcitonin.

- Bone resorption markers include urine and serum N-telopeptide, serum Ctelopeptide, urine pyridinoline, and urine deoxypyridinoline, urine hydroxyproline
- Bone formation markers include serum osteocalcin, serum bone-specific alkaline phosphatase, and serum procollagen type 1 N terminal propeptide. [1-3,25-26]

Stopping Therapy

The evidence based on duration of treatment is limited. Alendronate and Risedronate appear to be safe and effective for up to 10 years in most patients, but some randomized trial with alendronate showed that overall fracture rates were similar in those given 5 years. So stopping the drug after 5 years does not significantly increase fracture risk but patients with very high fracture risk may benefit from continued therapy.[1-2, 25]

Osteoporosis is the most common bone disease and affects million of People worldwide. Despite the availability of excellent clinical tools to assess fracture risk and widely available drugs to reduce fracture risk, osteoporosis remains under diagnosed and undertreated. Bones become fragile and often diagnosed after a serious fracture. DEXA scan is the pivotal investigation for diagnosis of osteoporosis. Always secondary causes should be evaluated in diagnosing osteoporosis. It has no cure but preventable and effectively treatable with non-pharmacological intervention and pharmacological therapy.

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