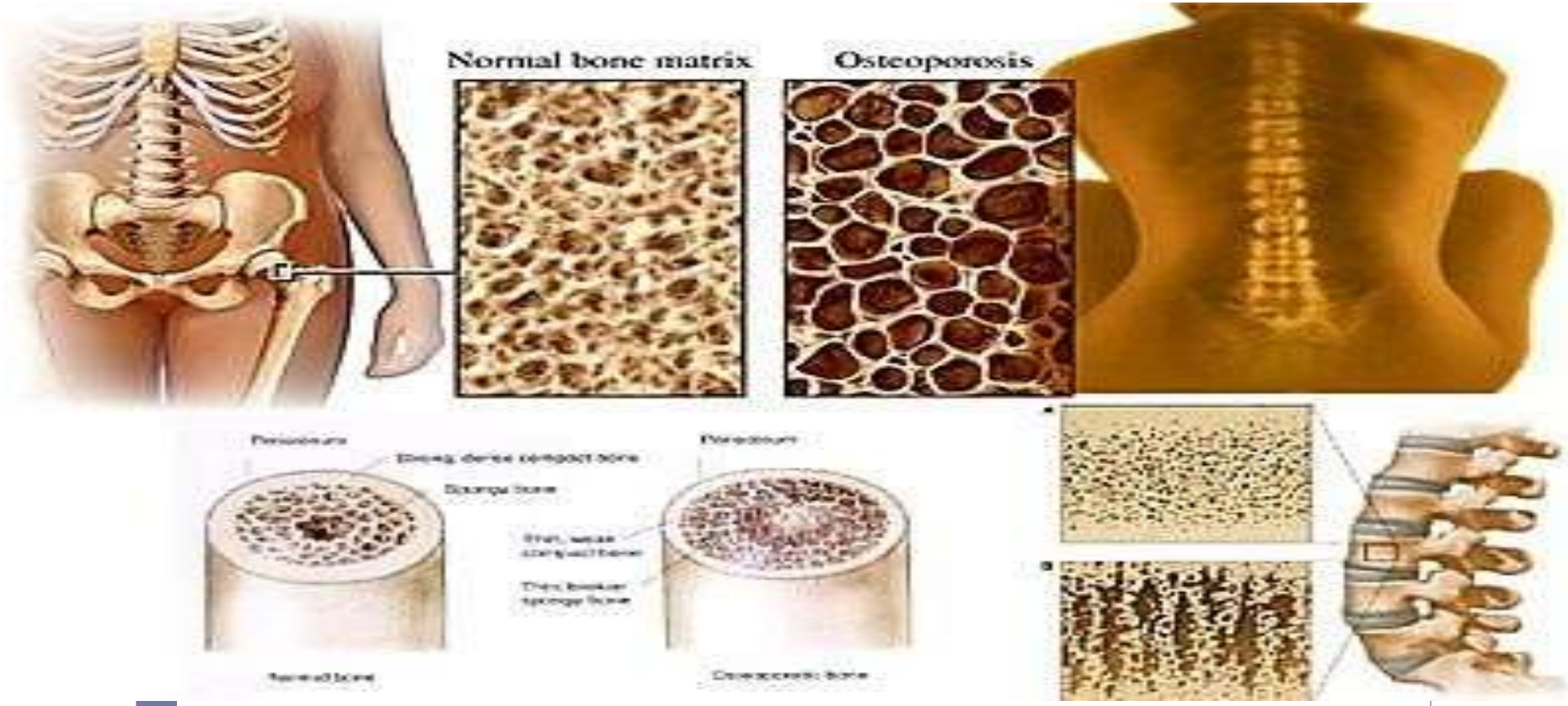


OSTEOPOROSIS

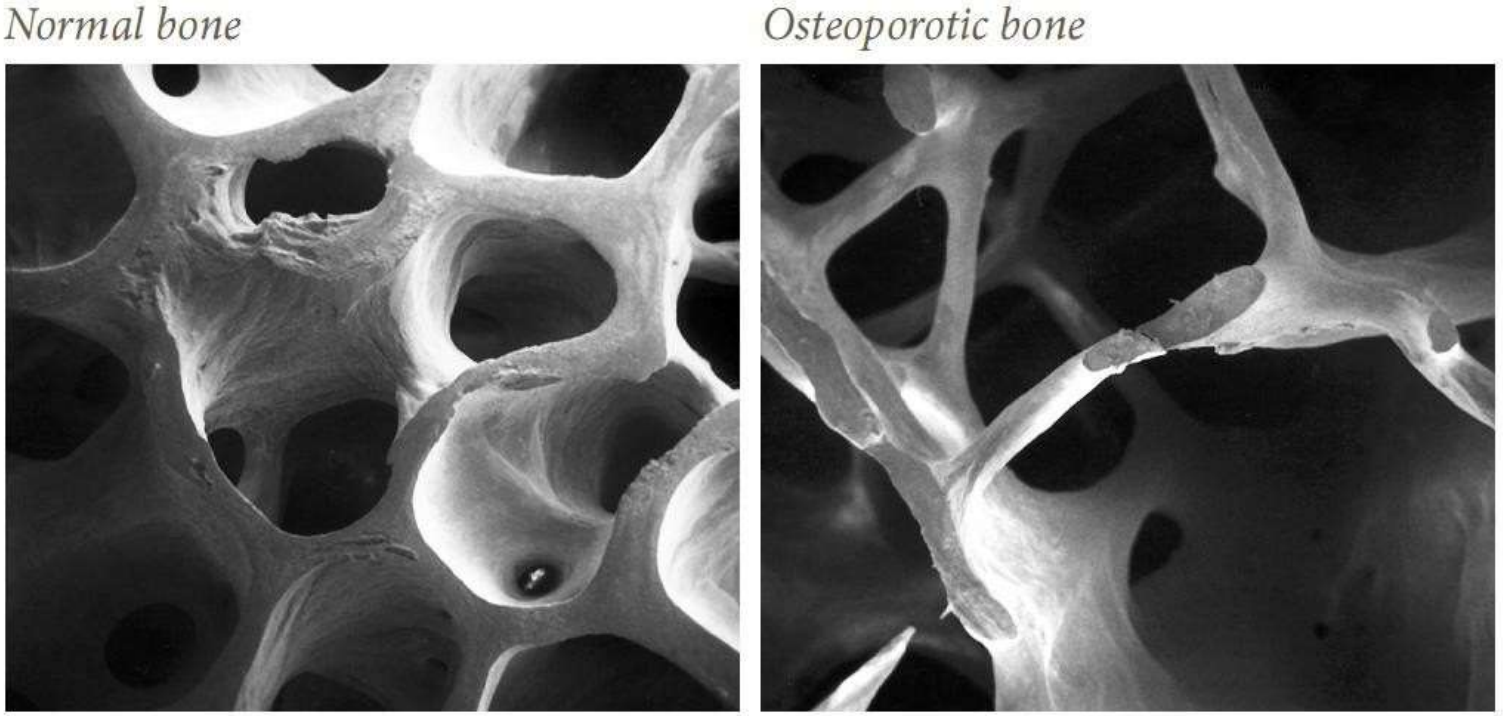
Dr R.Hari Babu
Professor& Head
Department of Pharmacy Practice
Chebrolu Hanumaiah Institute of Pharmaceutical Sciences

Definition

- **Osteoporosis** is a chronic, progressive disease characterized by:
  - low bone mass **(Osteopenia)**,
  - microarchitectural deterioration of bone tissue and decreased bone strength,
  - bone fragility
  - consequent increase in fracture risk;

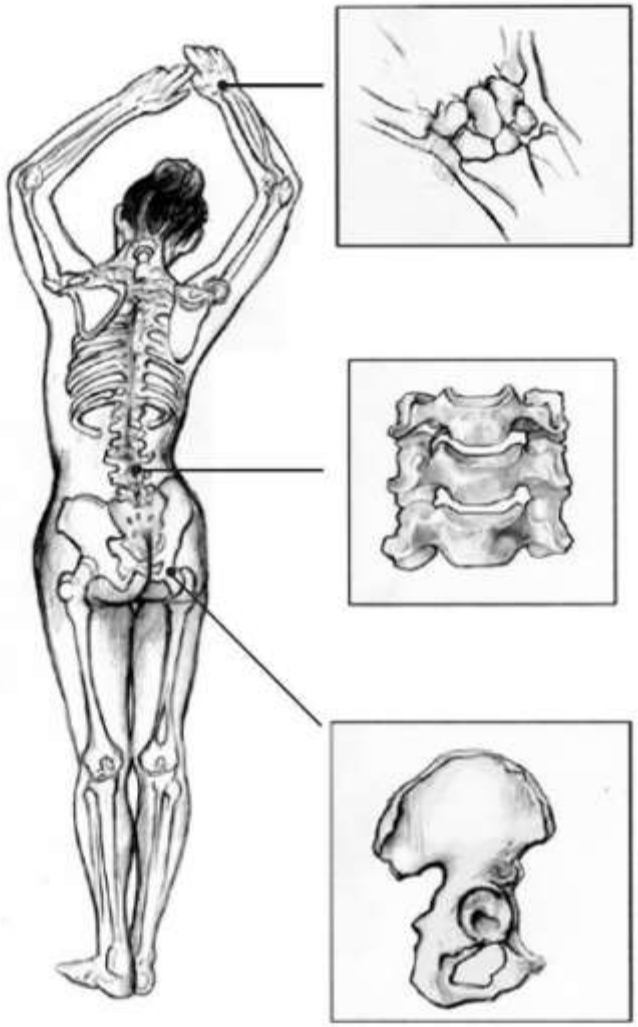
  According to the WHO diagnostic classification, osteoporosis is defined by bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the young normal mean reference population (T-score at or below -2.5).

- Figure shows the changes within cancellous bone as a consequence of bone loss. Individual trabecular plates of bone are lost, leaving an architecturally weakened structure with significantly reduced mass.



Medical impact

- Osteoporosis is a silent disease until it is complicated by fracture.
- Fractures can occur following minimal trauma.
- Osteoporosis can be prevented and can be diagnosed and treated before any fracture occurs.
- The most common fractures are those of the
  - Vertebrae (spine)
  - Proximal femur (hip)
  - Distal forearm (wrist).



Epidemiology

- Osteoporosis affects 200 million women worldwide. In fact, approximately 10% of 60 year old women have osteoporosis. This increases to two-thirds of women by the time women get to the age of 90 years.
- Fragility or low trauma wrist and vertebral fractures are common throughout adulthood, whereas hip fractures are more common in seniors.

Epidemiology

- Osteoporosis affects an enormous number of people, of both sexes and all races, and its prevalence will increase as the population ages.
- Based on data from the National Health and Nutrition Examination Survey III (NHANES III), NOF has estimated that more than 9.9 million Americans have osteoporosis and an additional 43.1 million have low bone
- Osteoporosis is less frequent in African Americans, those with osteoporosis have the same elevated fracture risk as Caucasians.
- About one out of every two Caucasian women will experience an osteoporosis-related fracture at some point in her lifetime, as will approximately one in five men.

Epidemiology

It is estimated that 50% of women over age 50 will develop a fracture in their remaining lifetime and the annualized risk increases with age. Twenty-five percent of women over age 50 will experience an osteoporotic vertebral fracture, so that by age 75 more than one in three women have sustained at least one vertebral fracture.

Relative Risk of Fracture at Various Sites in the Presence of a Radiographic Vertebral Compression Deformity

Site of Subsequent Fracture	Relative Risk (95% CI)
Vertebral	5.4 (4.4, 6.6)
Hip	2.8 (2.3, 3.4)
Any non-vertebral site	1.9 (1.7, 2.1)

Etiology

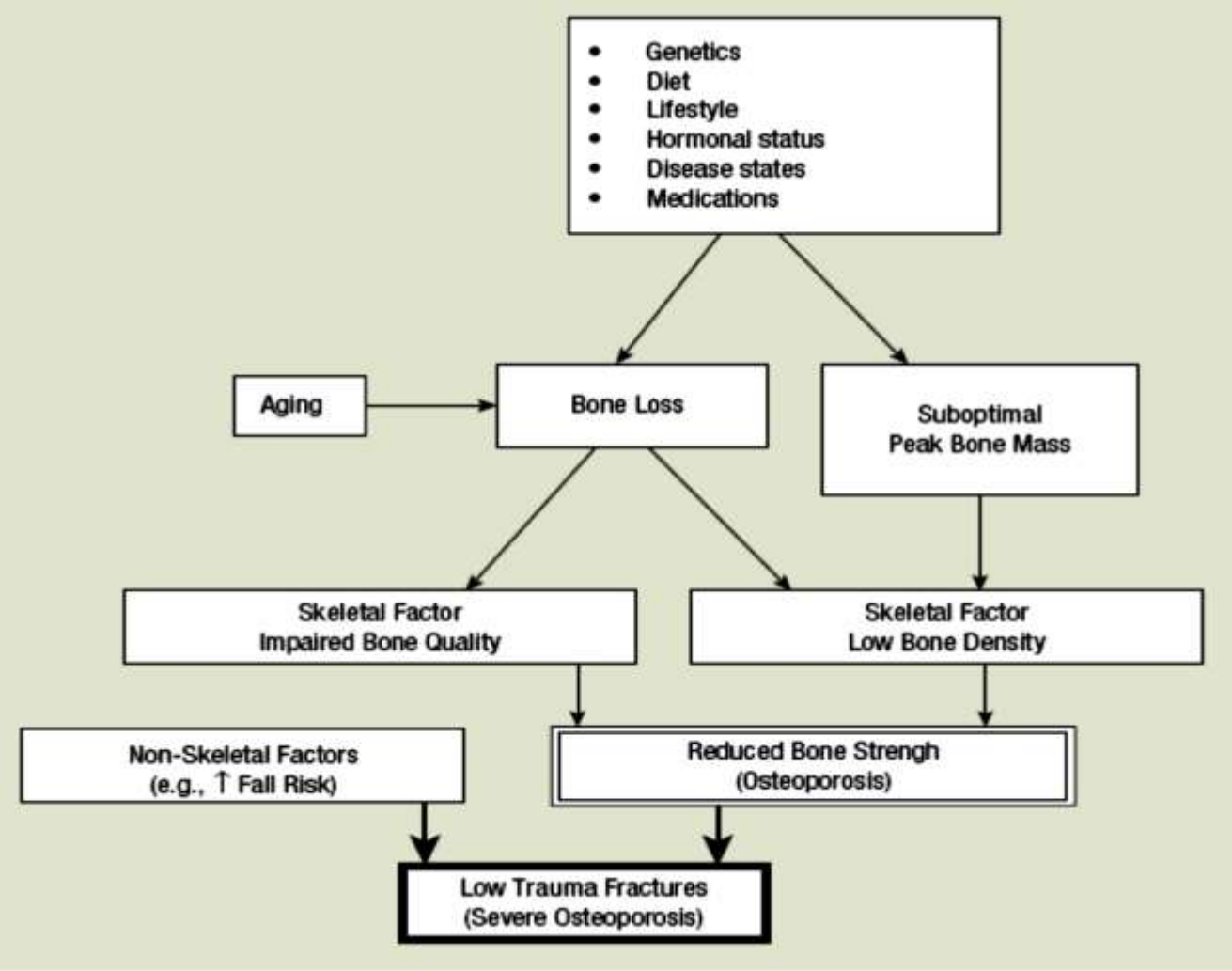
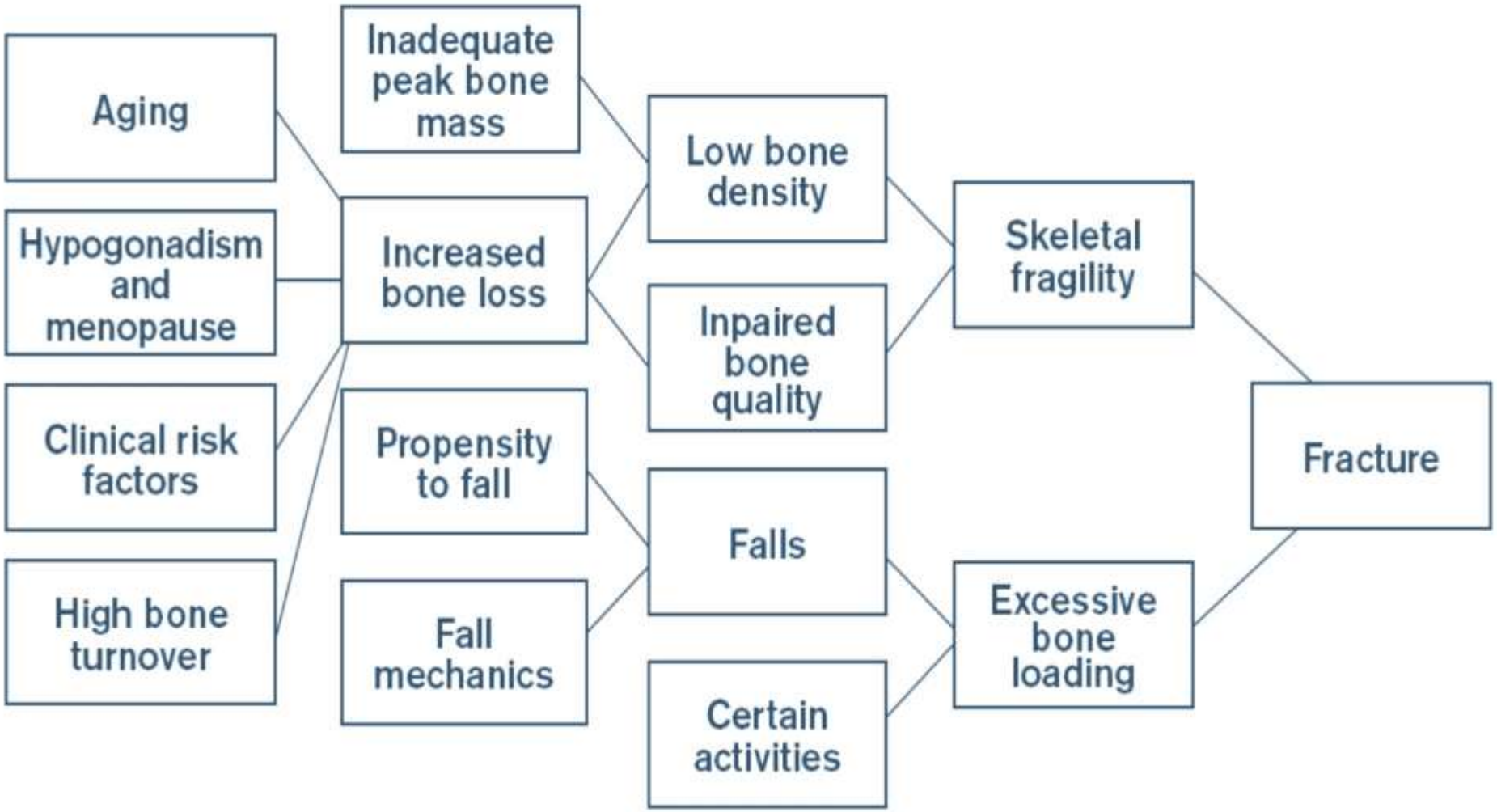

Genetics
Diet
Lifestyle
Hormonal status
Disease states
Medications
Aging
Bone Loss
Suboptimal
Peak Bone Mass
Skeletal Factor
Impaired Bone Quality
Skeletal Factor
Low Bone Density
Non-Skeletal Factors
(e.g., ↑ Fall Risk)
Reduced Bone Strengh
(Osteoporosis)
Low Trauma Fractures
(Severe Osteoporosis)

FIGURE 2. Pathogenesis of Osteoporosis-Related Fractures



Protective Estrogen role in bone remodeling

- Estrogen has many positive effects on the bone remodeling process.
- Most of its actions help to maintain a normal bone resorption rate:
  - suppresses proliferation & differentiation of osteoclasts & ↑ osteoclast apoptosis
  - ↓ production of several cytokines that are potent stimulators of osteoclasts including ILs 1 & 6,&TNF factor-α.
  - ↓ production of RANKL & ↑ production of OPG; both of which ↓ osteoclastogenesis
- Note:
  - mature osteoclasts (bone resorbing cells)
  - osteoblast (bone-forming cells)
  - Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL)
  - osteoprotegerin (OPG)

VITAMIN D, PTH, & Ca++

- Vitamin D and PTH maintain calcium homeostasis
- The most abundant source of vitamin D is the endogenous production from exposure to ultraviolet B light
- Dietary vitamin D sources include **cholecalciferol** & **ergocalciferol** (vitamin D2)
- conversion of cholecalciferol & ergocalciferol to 25-hydroxyvitamin D [25(OH) D] (**calcidiol**) occurs in the liver & then PTH stimulates conversion of 25(OH) D via 25(OH) D-1α-hydroxylase to its final active form, 1α,25-dihydroxyvitamin D (**calcitriol**), in the kidney
- Calcitriol binds to the intestinal vitamin D receptor → ↑ calcium binding protein → ↑ calcium & phosphorous intestinal absorption

VITAMIN D, PTH, & Ca++ (cont'd)

- Calcium absorption under normal conditions is ~ 30-40%
- ↓ to 10% to 15% with low vitamin D concentrations
- ↑ PTH concentrations secondary to hypocalcemia ↑ kidney calcitriol production & calcium reabsorption by the kidney
- PTH concentrations also ↑ when vitamin D concentration falls < ~30 ng/mL, the minimum normal therapeutic vitamin D concentration
- Sometimes increased fractional calcium absorption is insufficient → bone resorption is needed
- Together, PTH & calcitriol increase osteoclast activity → releasing calcium from bone to restore calcium homeostasis

Osteoporosis Categories

1. Postmenopausal Osteoporosis.
2. Male Osteoporosis
3. Age Related Osteoporosis.
4. Secondary Osteoporosis (disease or medication)
   - Hyperthyroidism
   - Renal disease.
   - Chronic obstructive pulmonary disease.

PATHOPHYSIOLOGY

POSTMENOPAUSAL OSTEOPOROSIS

- **Accelerated bone loss** during perimenopause & postmenopause due to ↑ resorption mainly as a result of the **loss in ovarian estrogen production**
- →↑proliferation, differentiation, & activation of new osteoclasts & prolongation of survival of mature osteoclasts
- Number of remodeling sites ↑ & resorption pits are deeper & inadequately filled by normal osteoblastic function
- Significant bone density is lost & bone architecture is compromised
- Trabecular bone is most susceptible leading to vertebral & wrist fractures

MALE OSTEOPOROSIS

- Men are at a lower risk for developing osteoporosis &osteoporotic fractures because of larger bone size, greater peak bone mass, & fewer falls.
- However, men have a higher mortality rate after fractures
- The etiology of male osteoporosis tends to be multifactorial with secondary causes & aging being the most common contributing factors
- In young & middle-age men, hypogonadism is the most common

AGE-RELATED OSTEOPOROSIS

- Occurs in seniors mainly as a result of hormone, Ca++, & vitamin D deficiencies →↑ bone turnover rate in combination with ↓osteoblast bone formation

- Hip fracture risk ↑dramatically as a consequence of the cumulative loss of cortical & trabecular bone & ↑risk for falls

Consequences of osteoporosis

- The most common osteoporosis-related fractures are those of the **vertebrae, proximal femur, & distal radius** (wrist or Colles fracture)
- Depression is common
- Symptomatic vertebral fractures can cause significant pain & physical deformity
- Patients with severe kyphosis can experience respiratory problems as a result of compression of the thoracic region & GI complications
- After a hip fracture, only 33-40% of patients regain their ability to perform basic activities of daily living,
- 14% to 36% will die within 1 year after a hip fracture

Risk Assessment

- All postmenopausal women and men age 50 and older should be evaluated clinically for osteoporosis risk in order to determine the need for BMD testing and/or vertebral imaging

Conditions, Diseases & Medications That Cause or Contribute to Osteoporosis & Fractures (NOF, 2014)

Lifestyle factors		
Low calcium intake	Vitamin D insufficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum (in antacids)
Alcohol (3 or more drinks/d)	Inadequate physical activity	Immobilization
Smoking (active or passive)	Falling	Thinness

Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan syndrome	Riley-Day syndrome
Hemochromatosis	Menkes steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Premature ovarian failure
Anorexia nervosa and bulimia	Premature menopause	Athletic amenorrhea

Endocrine disorders		
Adrenal insufficiency	Cushing's syndrome	Central Adiposity
Diabetes mellitus (Types 1 & 2)	Hyperparathyroidism	Thyrotoxicosis
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
GI surgery	Pancreatic disease	
Hematologic disorders		
Multiple myeloma	Monoclonal gammopathies	Sickle cell disease
Hemophilia	Leukemia and lymphomas	Systemic mastocytosis
Thalassemia		
Rheumatologic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Other rheumatic and autoimmune diseases		
Central nervous system disorders		
Epilepsy	Parkinson's disease	Stroke
Multiple sclerosis	Spinal cord injury	
Miscellaneous conditions and diseases		
AIDS/HIV	Congestive heart failure	Muscular dystrophy
Alcoholism	Depression	Post-transplant bone disease
Amyloidosis	End stage renal disease	Sarcoidosis
Chronic metabolic acidosis	Hypercalciuria	Weight loss
Chronic obstructive lung disease	Idiopathic scoliosis	

Medications		
Aluminum (in antacids)	Cyclosporine A and tacrolimus	Proton pump inhibitors
Anticoagulants (heparin)	Depo-medroxyprogesterone (premenopausal contraception)	Selective serotonin reuptake inhibitors
Anticonvulsants	Glucocorticoids (≥ 5 mg/d prednisone or equivalent for ≥ 3 months)	Tamoxifen® (premenopausal use)
Aromatase inhibitors	GnRH (Gonadotropin releasing hormone) antagonists and agonists	Thiazolidinediones (such as Actos® and Avandia®)
Barbiturates	Lithium	Thyroid hormones (in excess)
Cancer chemotherapeutic drugs	Methotrexate	Parenteral nutrition

Risk Factors for Falls

Since the majority of osteoporosis-related fractures result from falls, it is also important to evaluate risk factors for falling

Environmental risk factors
Lack of assistive devices in bathrooms
Loose throw rugs
Low level lighting
Obstacles in the walking path
Slippery outdoor conditions

Risk Factors for Falls (cont'd)

Medical risk factors	
Age	Medications causing oversedation (narcotic analgesics, anticonvulsants, psychotropics)
Anxiety and agitation	Orthostatic hypotension
Arrhythmias	Poor vision and use of bifocals
Dehydration	Previous fall
Depression	Reduced problem solving or mental acuity and diminished cognitive skills
Female gender	Urgent urinary incontinence
Impaired transfer and mobility	Vitamin D insufficiency [serum 25-hydroxyvitamin D (25(OH)D) < 30 ng/ml (75 nmol/L)]
Malnutrition	

Neurological and musculoskeletal risk factors	
Kyphosis	Reduced proprioception
Poor balance	Weak muscles/sarcopenia
Impaired transfer and mobility	Deconditioning
Diseases listed in Table 1	

Risk factors included in the WHO 10-year fracture risk assessment model

TABLE 3: Risk Factors Included in the WHO Fracture Risk Assessment Model

Clinical Risk Factors Included in the FRAX Tool	
• Current age	• Rheumatoid arthritis
• Gender	• Secondary osteoporosis: Type1 (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption and chronic liver disease
• A prior osteoporotic fracture (including clinical and asymptomatic vertebral fractures)	• Parental history of hip fracture
• Femoral neck BMD	• Current smoking
• Low body mass index (BMI, kg/m^2)	• Alcohol intake (3 or more drinks/d)
• Oral glucocorticoids ≥5 mg/d of prednisone for≥3 months (ever)	

this set of risk factors increases risk independently of BMD and can be combined with BMD measurements and used to assess an individual patient's risk of future fracture.

Diagnosis

- The diagnosis of osteoporosis is established by:
- measurement of BMD or
- occurrence of adulthood hip or vertebral fracture in the absence of major trauma (such as a motor vehicle accident or multiple story fall).
  - BMD
  - Vertebral imaging
  - Biochemical markers of bone turnover

Central Dual-Energy X-Ray Absorptiometry (hip, spine)

- can be used to **assess fracture risk, establish the diagnosis & severity of osteoporosis**
- sometimes confirm osteoporosis as causative for low-trauma fractures
- BMD is expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm^2)
- is considered the **gold standard** for measuring BMD because of its high precision, short scan times, low radiation dose (comparable to the average daily dose from natural background), & stable calibration
- **measurement of both lumbar spine & proximal femur or total hip BMD are recommended with the lowest BMD value used for diagnosis**

DXA

DXA

Name: Express Scans, 2
Patient ID:
DOB: August 24, 1944

Sex: Female
Ethnicity: White

Height: 65.0 in
Weight: 150.0 lb
Age: 61

Referring Physician:

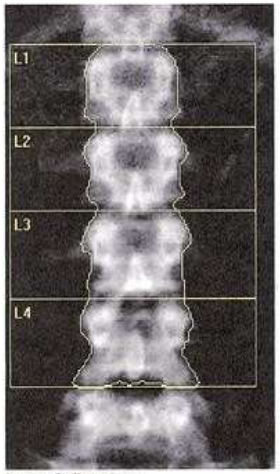


Image not for diagnostic use
k = 1.138, d0 = 48.0
116 x 149

Scan Information:

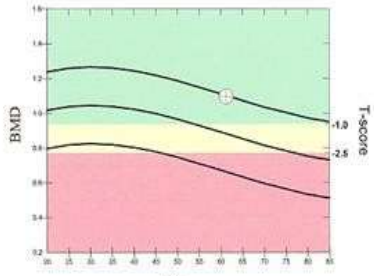
Scan Date: November 12, 2005 ID: A11120501
Scan Type: x Lumbar Spine
Analysis: November 12, 2005 09:48 Version 12.4:3
Lumbar Spine
Operator:
Model: Discovery C (S/N 81202)
Comment:

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
L1	14.41	14.44	1.002	0.7	108	2.0	129
L2	15.27	16.33	1.069	0.4	104	1.8	123
L3	16.99	19.69	1.159	0.7	107	2.2	127
L4	18.74	21.27	1.135	0.2	102	1.8	121
Total	**65.41**	**71.72**	**1.096**	**0.4**	**105**	**1.9**	**124**

Total BMD CV 1.0%, ACF = 1.000, BCF = 1.000, TH = 3.855
WHO Classification: Normal
Fracture Risk: Not Increased

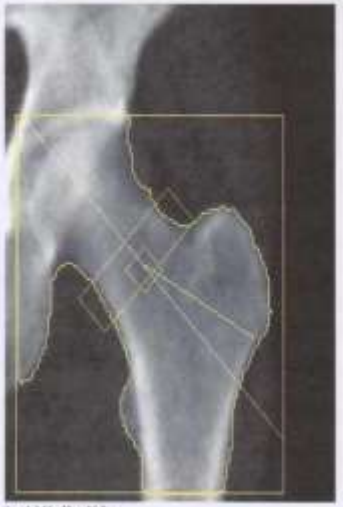
Total



Fracture Risk
Not Increased Increased High
T-score vs. White Female; Z-score vs. White Female. Source Hologic

Physician's Comment:

HOLOGIC®



k = 1.141, d0 = 46.9
103 x 117
NECK: 49 x 15
DAP: 1.5 cGy*cm²

Scan Information:

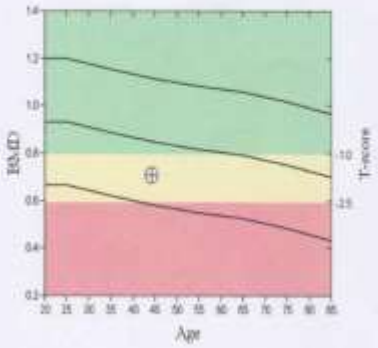
Scan Date: 22 January 2015 ID: A01221507
Scan Type: x Left Hip
Analysis: 22 January 2015 12:17 Version 13.4.2:3
Hip
Comment:

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
Neck	5.64	3.99	0.707	-1.6	76	-1.0	83
Troch	11.98	8.04	0.671	-0.8	86	-0.6	90
Inter	24.80	27.90	1.125	-0.4	94	-0.3	96
Total	42.42	39.92	0.941	-0.6	91	-0.4	94
Ward's	1.16	0.60	0.521	-1.9	66	-0.9	81

Total BMD CV 1.0%, ACF = 1.048, BCF = 1.021, TH = 6.024
WHO Classification: Osteopenia

Neck



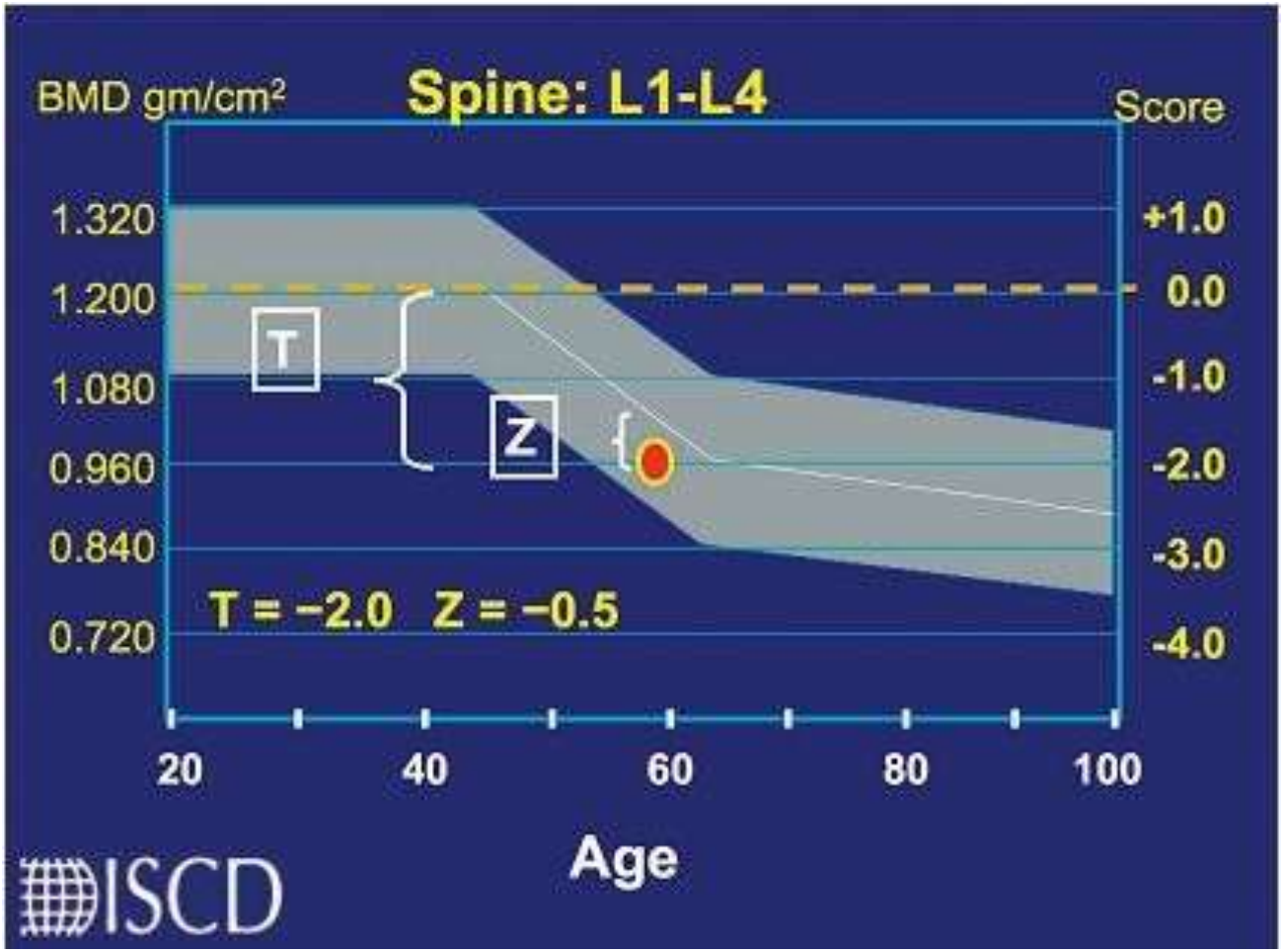
Comment:

Central DXA (cont'd)

- The **T-score** is a comparison of a person's bone density with that of a healthy 30-year-old of the same sex.
- The T-score is the number of standard deviations from the mean of the reference population
- The **Z-score** compares the patient's BMD to the mean BMD for sex, age and ethnicity-matched reference population & is usually low when secondary causes of osteoporosis are present
- The difference between the patient's BMD and the mean BMD of the reference population, divided by the standard deviation (SD) of the reference population, is used to calculate T-scores and Z-scores.

Z- and T-Score

Areal BMD is expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm^2)



Defining Osteoporosis by BMD

WHO Definition of Osteoporosis Based on BMD		
Classification	**BMD**	**T-score**
Normal	Within 1 SD of a young-adult reference population	T-score at -1.0 and above
Low Bone Mass (Osteopenia)	Between 1.0 and 2.5 SD below that of a young-adult reference population	T-score between -1.0 and -2.5
Osteoporosis	2.5 SD or more below that of a young- adult reference population	T-score at or below -2.5
Severe or Established Osteoporosis	2.5 SD or more below that of a young- adult reference population	T-score at or below -2.5 with one or more fractures

Note: Although these definitions are necessary to establish the presence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

In premenopausal women, men less than 50 years of age and children, the WHO BMD diagnostic classification should not be applied.

Indications for BMD Testing – NOF 2014

Table 7: 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 postmenopausal women, women in the menopausal transition and men age 50 to 69 with clinical risk factors for fracture
• Adults who have a fracture 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 ≥ three months) associated with low bone mass or bone loss

Vertebral imaging

- Independent of BMD, age and other clinical risk factors, radiographically confirmed vertebral fractures (even if completely asymptomatic) are a sign of impaired bone quality and strength, and a strong predictor of new vertebral and other fractures.
- The presence **of a single vertebral fracture** increases the risk of subsequent fractures 5-fold and the risk of hip and other fractures 2- to 3- fold.
- Vertebral imaging can be performed using a lateral thoracic and lumbar spine x-ray or lateral vertebral fracture assessment (VFA), available on most modern DXA machines.
- VFA can be conveniently performed at the time of BMD assessment, while conventional x-ray may require referral to a standard x-ray facility.

Vertebral imaging (NOF 2014)

- 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.
- Most vertebral fractures are asymptomatic when they first occur and often are undiagnosed for many years.
- Proactive vertebral imaging is the only way to diagnose these fractures. The finding of a previously unrecognized vertebral fracture may change the diagnostic classification, alter future fracture risk calculations and affect treatment decisions.

Indications for vertebral imaging

Table 7: Indications for Vertebral Imaging

Consider vertebral imaging tests for the following individuals:***
• All women age 70 and older and all men age 80 and older if BMD T-score at the spine, total hip or femoral neck is ≤ -1.0.
• Women age 65 to 69 and men age 70 to 79 if BMD T-score at the spine, total hip or femoral neck is ≤ -1.5
• Postmenopausal women and men age 50 and older with specific risk factors: ▪ Low trauma fracture during adulthood (age 50) ▪ Historical height loss of 1.5 inches or more (4 cm)* ▪ Prospective height loss of 0.8 inches or more (2 cm)** ▪ Recent or ongoing long term glucocorticoid treatment

* Current height compared to peak height during young adulthood

** Cumulative height loss measured during interval medical assessment

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

Bone biomarkers

- resorption markers: serum C-telopeptide (CTX) and urinary N-telopeptide (NTX)
- formation markers: serum bone specific alkaline phosphatase (BSAP), osteocalcin (OC) and aminoterminal propeptide of type I procollagen (PINP)] are best collected in the morning while patients are fasting.
- **Biochemical markers of bone turnover may:**
- • Predict risk of fracture independently of bone density in untreated patients.
- • Predict rapidity of bone loss in untreated patients.
- • Predict extent of fracture risk reduction when repeated after 3-6 months of treatment with FDA-approved therapies.
- • Predict magnitude of BMD increases with FDA-approved therapies.
- • Help determine adequacy of patient compliance and persistence with osteoporosis therapy.
- • Help determine duration of 'drug holiday' and when and if medication should be restarted (Data are quite limited to support this use, but studies are underway).

Clinical Presentation of Osteoporosis

General

- Many patients only present after fracture
- Fractures can occur after bending, lifting, or falling, or independent of any activity

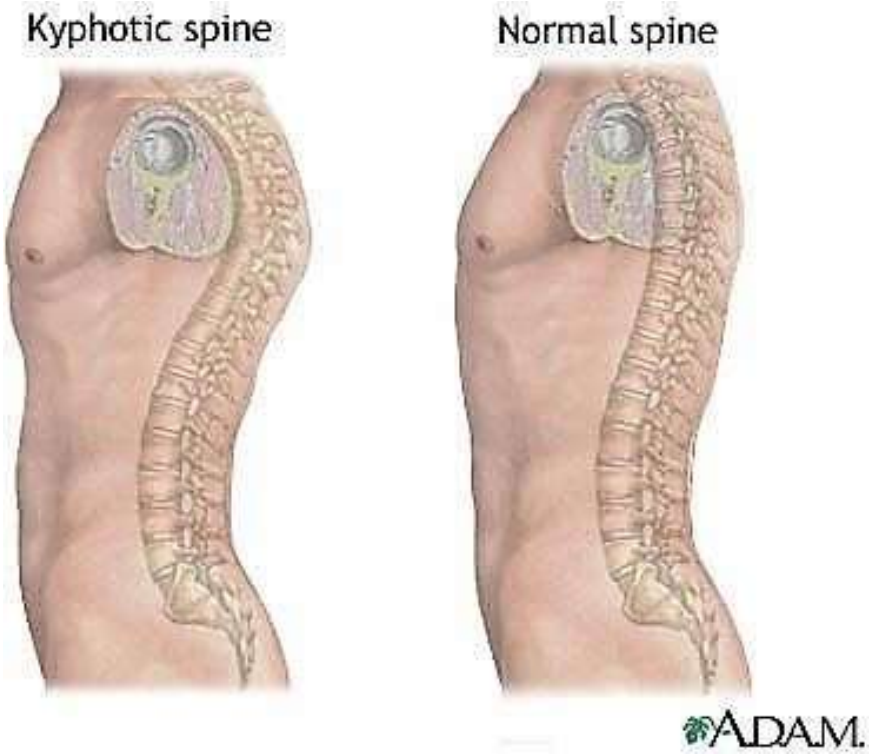
Symptoms

- Pain
- Immobility
- Depression, fear,& low self-esteem from physical limitations & deformities
- 2/3 of vertebral fractures are asymptomatic

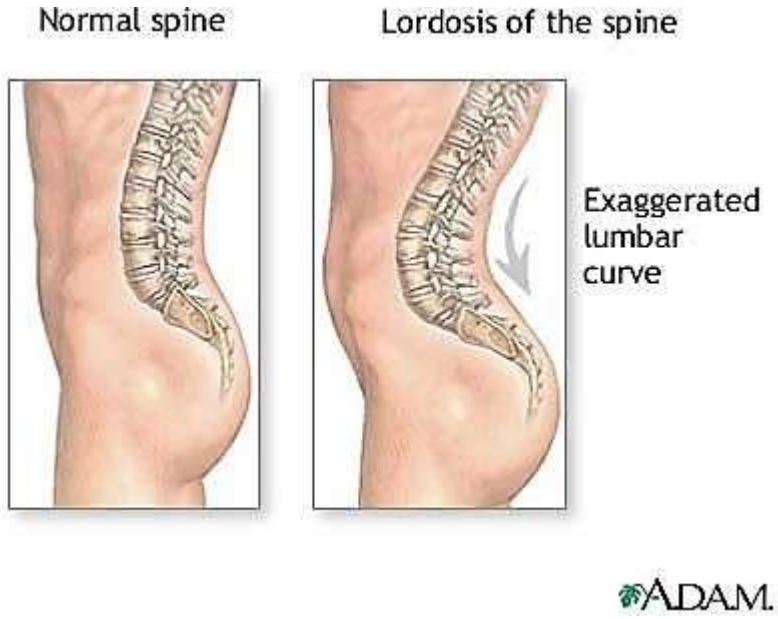
Signs

- Shortened stature (>1.5" loss), kyphosis, or lordosis
- Vertebral, hip, wrist, or forearm fracture
- Low bone density on radiography

Kyphosis & lordosis of the spine



Kyphotic curves refer to the outward curve of the thoracic spine



Lordotic curves refer to the inward curve of the lumbar spine

Clinical Presentation of Osteoporosis (cont'd)

Laboratory tests

- Routine tests to detect a possible secondary cause: CBC, LFT, KFT, Ca++, Ph, AlkPh, albumin, TSH, free testosterone, 25(OH)vitamin D, & 24-hour urine concentrations of Ca++ & Ph
- Urine or serum biomarkers (e.g., (NTX), osteocalcin) are sometimes used, especially to determine if high bone turnover exists

Other diagnostic tests

- Spine & hip bone-density measurement using DXA
- Radiograph to confirm vertebral fracture

DXA, dual-energy x-ray absorptiometry;

NTX, N-terminal crosslinking telopeptide of type I collagen

PATIENT ASSESSMENT

- **Bone pain, postural changes** (i.e., kyphosis), & **loss of height** are simple useful physical examination findings
- Height loss >1.5 inches from the tallest mature height is considered significant & warrants further investigation
- A **spine radiograph** can confirm **vertebral fractures**
- **Low bone density or osteopenia** reported on routine radiographs requires an evaluation for osteoporosis
- Patients can be assessed with **risk factor assessment, osteoporosis questionnaires, peripheral & central DXA, & biomarkers**

Risk factor assessment

Major risk factors by the NOF:

- Current smoker
- low body weight (<127 lb (~50Kg) in postmenopausal women)
- history of osteoporotic fracture in a first degree relative
- personal history of low-trauma fracture as an adult

Other identified independent risk factors:

- age
- high bone turnover
- low body mass index (<19 kg/m^2)
- rheumatoid arthritis
- glucocorticoid use

DIAGNOSIS OF OSTEOPOROSIS

- The diagnosis of osteoporosis is based on a low-trauma fracture or central hip and/or spine DXA usingWHOT-score thresholds.
  - Osteopenia or low bone mass is a T-score of –1 to –2.4
  - Osteoporosis is a T-score at or below –2.5.

- Although these definitions are based on data from postmenopausal white women, they are applied to other racial/ethnic groups and senior men.

- The International Society for Clinical Densitometry recommends the presence of risk factors in addition to a low T-score before the diagnosis of osteoporosis can be made in men ages 50 to 65 years.

PREVENTION & TREATMENT

DESIRED OUTCOMES

- **The primary goal should be prevention -** optimizing skeletal development & peak bone mass accrual in childhood, adolescence, & early adulthood

- **once osteopenia or osteoporosis develops**, the objective is to stabilize or improve bone mass & strength & prevent fractures

- **in pts. who have already suffered osteoporotic fractures,** ↓ future falls & fractures, improving functional capacity, ↓ pain & deformity,& improving quality of life

Guidelines for treatment of osteoporosis NOF-2014

Obtain a detailed patient history pertaining to clinical risk factors for osteoporosis-related fracture.

Perform physical examination to evaluate for signs of osteoporosis and its secondary causes.

Modify diet/supplements and other clinical risk factors for fracture.

Estimate patient's 10-year probability of hip and any major osteoporosis-related fracture using the US-adapted WHO algorithm.

Decisions on whom to treat and how to treat should be based on clinical judgment using this Guide and all available clinical information.

Consider FDA-approved medical therapies based on the following:

- A vertebral or hip fracture
- A DXA hip (femoral neck) or spine T-score ≤ -2.5
- Low bone mass and a US-adapted WHO 10-year probability of a hip fracture ≥ 3% or 10-year probability of any major osteoporosis-related fracture ≥ 20%
- Patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Consider non-medical therapeutic interventions:

- Modify risk factors related to falling
- Consider physical and occupational therapy including walking aids and hip pad protectors
- Weight-bearing activities daily

Patients not requiring medical therapies at the time of initial evaluation should be clinically re-evaluated when medically appropriate.

Patients taking FDA-approved medications should have laboratory and bone density re-evaluation after two years or more frequently when medically appropriate.

Nonpharmacologic Therapy (bone-healthy lifestyle changes)

- includes diet, smoking cessation, exercise, fall prevention, & hip protectors

Diet

- balanced in nutrients & minerals
- ↓ caffeine (2-4 servings/d),
- ↓ alcohol (1 drink/d for women & 2 drinks/d for men)
- ↓ sodium (<2.4 g/day) – why?
- ↓ cola & other carbonated beverages (caffeine & phosphoric acid content of cola beverages might cause bone loss by altering calcium balance)

Calcium

- Adequate intake is an essential component of all osteoporosis ***prevention*** & ***treatment*** strategies
- Achieving daily Ca++ requirements from Ca++-containing foods
- Some food sources are absorbed well but have low elemental Ca++ content (e.g., broccoli), or contain oxalic acid (e.g., spinach) or phytic acid (e.g., wheat bran) that bind Ca++ within the food & ↓ its absorption
- **lactose intolerance**: incidence in Asian (80%) & African American (50%) populations being much higher than in whites (10%) → lactose-reduced milk, lactose-free milk, yogurt with active cultures or Lactaid, along with other nondairy calcium-fortified products (e.g., orange juice, breakfast cereals) can be recommended

Calcium

- NOF supports Institute of Medicine (IOM) recommendations:
- men age 50-70 consume **1,000 mg per day of calcium**
- women age 51 and older and men age 71 and older **consume 1,200 mg per day of calcium**.
- There is no evidence that calcium intake in excess of these amounts confers additional bone strength. Intakes in excess of 1,200 to 1,500 mg per day may increase the risk of developing kidney stones, cardiovascular disease and stroke. The scientific literature is highly controversial in this area.

TABLE 93-4 Calcium and Vitamin D Recommendations

Group and Ages	Institute of Medicine Adequate Intake: *Elemental Calcium (mg)*[a]	Institute of Medicine Adequate Intake: *Vitamin D (units)*[a,b]
Infants		
Birth to 6 months	210	200
6–12 months	270	200
Children		
1–3 years	500	200
4–8 years	800	200
9–13 years	1,300	200
Adolescents/young adults		
14–18 years	1,300	200
Adults		
19–30 years	1,000	200
31–50 years	1,000	200
51–70 years	1,200	400
>70 years	1,200	600

[a]U.S. Institute of Medicine of the National Academy of Sciences recommends no more than 2500 mg/day elemental calcium and 2000 units/day vitamin D.

[b]Most experts believe the recommended Adequate Intakes for Vitamin D are too low.

TABLE 93-5 Elemental Calcium Content of Selected Foods and Beverages

Foods/Beverages	Elemental Calcium Content (mg)[a]
Milk (skim, low-fat, whole), 1 cup	276–309
Calcium-fortified soy milk, 1 cup	80–300
Calcium-fortified orange juice, 1 cup	300
Calcium-fortified cranberry juice, 1 cup	100
7UP Plus, 1 cup	100
Low-fat fruit yogurt, 1 cup	345
Frozen yogurt, 1 cup	180–240
Vanilla ice cream, 1 cup	176–200
Soft-serve vanilla ice cream, 1 cup	236
Swiss cheese, 1.5 oz.	336
Cheddar, mozzarella, or provolone cheese, 1.5 oz.	307–311
Ricotta cheese, ½ cup	255–335
Cottage cheese, 4 oz.	78–100
Fortified breakfast cereals	236–1,043
Fortified instant oatmeal	99–110
Figs, dried, 10	270
Collard greens, cooked, ½ cup	178
Broccoli, cooked, 1 cup	100–180
Soybeans, cooked, ½ cup	88–130
Okra, cooked, ½ cup	88
Bok choy, raw, 1 cup	160–250
Tofu, firm, ½ cup	253
Almonds, 1 oz.	75
Salmon, canned with bones, 3 oz.	170–210

[a]Food labels are based on a RDA of 1,000 mg/day; multiply percentage on package by 10 (e.g., product containing 30% calcium = 300 mg).

Data from www.health.gov/dietaryguidelines/dga2005/document/html/appendixB.htm.

Calcium

Estimating daily dietary calcium intake

STEP 1: Estimate calcium intake from calcium-rich foods*

Product	Servings/d		Estimated calcium/ serving, in mg		Calcium, in mg
Milk (8 oz.)	_____	x	300	=	_____
Yogurt (6 oz.)	_____	x	300	=	_____
Cheese (1 oz. or 1 cubic in.)	_____	x	200	=	_____
Fortified foods or juices	_____	x	80 to 1,000**	=	_____

STEP 2: Total from above + 250 mg for nondairy sources = total dietary calcium

Calcium, in mg

_____

* About 75 to 80 percent of the calcium consumed in American diets is from dairy products.
** Calcium content of fortified foods varies.

Vitamin D

- NOF guidelines recommend **800-1,000** International Units (IU) vitamin D daily for *adults age 50 years & >* in seniors 2,000 may be needed
- Institute of Medicine Dietary Reference Intakes for vitamin D are **600 IU per day until age 70 and 800 IU per day for adults age 71 years and older.**
- 3 main sources of vitamin D are: **sunlight, diet, & supplements**
- Because few foods are naturally high or fortified with vitamin D, most people, especially seniors, require supplementation

TABLE 93-6 Vitamin D Content of Selected Foods and Beverages

Foods/Beverages	Vitamin D (international units)[a]
Salmon, 3.5 oz	360
Mackerel, 3.5 oz	345
Tuna fish, canned in oil, 3 oz	200
Sardines, canned in oil, 1.75 oz	250
Cow's milk (all forms), 1 cup	100
Vitamin D fortified orange juice	100
Ready-to-eat-cereal (fortified), 1 cup	40
Margarine, 1 tablespoon	60
Egg, 1 whole (or egg yolk)	20
Liver, beef, cooked, 3.5 oz	15

[a]Food labels are based on a RDA of 400 units/day; multiply percentage on package by 4 (e.g., product f
containing 20% vitamin D = 80 units).

Data from http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp.

Treatment **of** Vitamin D **Deficiency**

- Adults who are vitamin D deficient may be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week
- or the equivalent daily dose (7,000 IU vitamin D2 or vitamin D3) for 8-12 wks to achieve a 25(OH)D blood level of approximately 30 ng/ml.

- This regimen should be followed by maintenance therapy of 1,500–2,000 IU/d or whatever dose is needed to maintain the target blood level.

Protein

- low protein intakes ↑ osteoporosis risk & higher protein intakes are protective against bone loss & fractures

Dietary Soy

- Isoflavone phytoestrogens are plant-derived compounds that possess weak estrogenic agonist & antagonist effects
- The most common source for isoflavone is dietary soy products.
- The evidence supporting a positive bone benefit from soy protein intake is conflicting, with some positive data with larger isoflavone intakes

Smoking Cessation

- Cigarette smoking is associated with up to an 80% ↑ relative risk for hip fracture
- Negative bone effects are due to:
  - ↓ in sex hormone concentrations,
  - ↓ intestinal Ca++ absorption
  - direct toxic effect on osteoblasts
- detrimental effects on neurovascular function

Exercise (weight bearing and muscle strengthening)

- can ↓ risk of falls & fractures by improving muscle strength coordination, balance,& mobility
- lack of exercise during growth can lead to:
  - suboptimal loading/straining,
  - ↓ stimulation of bone deposition,
  - ↓ peak bone mass
- All patients who are medically fit should be encouraged to perform a moderate-intensity **weight bearing activity** (e.g., walking, jogging, stair climbing) for at least 30 min. most days of the week & a **resistance activity** (e.g., weight machines, free weights, or elastic bands) at least twice per week for 20-30 min.

Pharmacological trearment

- Current FDA-approved pharmacological options for osteoporosis prevention &/or treatment are:
- Antiresorptive therapy:
  - Calcium and vitamin D supplements
  - bisphosphonates (alendronate, ibandronate,risedronate & zoledronic acid),
  - calcitonin,
  - estrogens &/or hormone therapy,
  - estrogen agonist/antagonist (raloxifene).
  - Denosumab.
- Anabolic Drugs: Teriparatide

Who Should Be Considered for Treatment?

- Postmenopausal women and men age 50 and older presenting with the following should be considered for treatment:
- A hip or vertebral fracture (clinically apparent or found on vertebral imaging).
- In patients with a hip or spine fracture, the T-score is not as important as the fracture itself in predicting future risk of fracture and anti-fracture efficacy from treatment.
- •T-score ≤ -2.5 at the femoral neck, total hip or lumbar spine.
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine) and a 10-year probability of a hip fracture ≥3 % or a 10-year probability of a major osteoporosis-related fracture ≥20 %

PHARMACOLOGIC THERAPY

Drug Treatments of First Choice

- Bisphosphonates are the prescription DOC
- Teriparatide, raloxifene,& calcitonin are alternative agents

- Duration of bisphosphonate therapy has not been defined, but safety data exist for periods of 7–10 years

- Short-term (18-24 months) teriparatide is used for severe osteoporosis & then followed by bisphosphonate therapy.

Calcium Supplementation

- Adequate calcium intake is considered the minimal standard for osteoporosis prevention and treatment and should be combined with vitamin D and osteoporosis medications when needed.
- Supplemental calcium intake will be needed in the majority of people with or at risk for osteoporosis

- ***Efficacy:*** ↑ BMD, but fracture prevention is minimal
  - Calcium's BMD effects are less than other antiresorptive & osteoporosis medications

- ***Non-bone benefits***: ↓ blood pressure, cholesterol, & colorectal cancer risk, the last being controversial

Ca supplementation (cont'd)

- ***Adverse Events/Precautions.***
  - most common: constipation →↑ water intake, dietary fiber, & exercise

    if still unresolved, smaller & > frequent administration or lower total daily dose can be tried
  - calcium carbonate can create gas & cause stomach upset → calcium citrate has fewer GI side effects
  - Ca++ rarely causes kidney stones →↑ fluid intake & ↓ salt intake

Ca supplementation (cont'd)

Administration.

- Because fractional Ca++ absorption is dose-limited, maximum single doses of 600 mg or < of elemental Ca++ are recommended.
- Calcium carbonate is the salt of choice as it contains the highest amount of elemental Ca++ & is the least expensive
- Calcium carbonate tablets should be taken with meals to ↑ absorption
- **Calcium citrate** absorption is acid-independent & need not be administered with meals.

Vitamin D Supplementation

- Vitamin D intake is critical for the prevention and treatment of osteoporosis because it maximizes intestinal calcium absorption.

- ***Efficacy:*** While several studies have demonstrated a beneficial effect of vitamin D on **fractures and falls**, not all studies have demonstrated a beneficial effect (due to differences in vitamin D dosing, concomitant calcium administration, adherence, etc.)

Vitamin D Supplementation

Administration.

- Seniors & patients being treated for osteoporosis: min. 800 units through food & supplementation
- **Cholecalciferol (vitamin D3**) is > efficient than **ergocalciferol (vitamin D2)** & is the preferred form
- In patients. with measured insufficient 25(OH) D concentrations, higher daily intakes of vitamin D may be needed
- half-life of vitamin D is about 1 month → ~ 3 months of therapy are required before a new steady state is achieved & repeat 25(OH) D concentration can be obtained
- In pts. with severe hepatic or renal disease, the **activated form of vitamin D (calcitriol)** might be more appropriate
- Some experts believe that the upper tolerable limit for vitamin D should be raised and that the recommended daily allowance for vitamin D should be 2,000 units per day

Bisphosphonates

- mimic pyrophosphate, an endogenous bone resorption inhibitor
- all bisphosphonates become incorporated into bone, giving them long biologic half-lives of up to 10 years.
- **alendronate**, **risedronate**, **oral ibandronate,** and **zoledronic acid** are currently FDA indicated for the prevention & treatment of postmenopausal osteoporosis
- **IV ibandronate is** indicated only for treatment of postmenopausal women
- **zoledronic acid, risedronate & alendronate** are also FDA indicated in male & glucocorticoid-induced osteoporosis

Bisphosphonates (Bis) (cont'd)

***Administration*.**

- bioavailability is very poor + GI side effects → each oral dose should be taken with at least 6 ounces of **plain tap water** (~300 ml) (not coffee, juice, mineral water, or milk) **at least 30 (60 for ibandronate) min.** before consuming any food, supplement (including Ca++ & vit. D), or medication.
- The tablets should be swallowed whole without chewing or sucking.
- Administration should be with water only and not combined with other fluids.
- weekly, raspberry flavored, oral solution only needs to be taken with 2 ounces of water & can be used for pts. with swallowing difficulties
- pt. should also **remain upright** (i.e., either sitting or standing) **for at least 30 min. after alendronate & risedronate &1 hour after ibandronate**
- **Before IV Bis are used, the pt.'s serum Ca++ level must be normal**
- The quarterly ibandronate injection is given IV over 15-30 sec .
- Once-yearly administration of zoledronic acid should be infused over at least 15 min.

Alendronate

- This bisphosphonate, marketed as Fosamax®, is approved as an oral tablet in both the United States and Canada for postmenopausal

- For osteoporosis prevention (5 mg/d or 35 mg/wk) and **treatment** (10 mg/d or 70 mg/wk).

- Alendronate is also available in a single weekly oral tablet of 70 mg with 5,600 IU of vitamin D (Fosamax® Plus D; Fosavance®).

Risedronate

This bisphosphonate, marketed as Actonel®, is approved in the United States and Canada for the **prevention and treatment** of postmenopausal osteoporosis in oral tablet doses of 5 mg/day, 35 mg/week, 75 mg on 2 consecutive days once a month, and 150 mg/month.

Ibandronate

- Oral Ibandronate, marketed as Boniva®, is approved as a 2.5-mg tablet once a day, as well as a 150-mg tablet once a month for the prevention and treatment of postmenopausal osteoporosis.

- It is also approved in an IV formulation at a 3-mg dose every 3 months (administered by a healthcare professional) for the **treatment of postmenopausal osteoporosis.**

Zoledronic acid (Most Potent Bisphosphonate)

- The bisphosphonate zoledronic acid, marketed as Reclast® in the United States and Aclasta® in Canada.
- FDA-approved for:
  - **osteoporosis treatment and prevention** in postmenopausal women.
  - to improve bone mass in men with osteoporosis,
  - prevention and treatment of osteoporosis in men and women expected to be on glucocorticoid therapy for at least 12 months.
  - prevention of new clinical fractures in patients (both women and men) who have recently had a low-trauma (osteoporosis-related) hip fracture.

Zoledronic acid

- The annual 5-mg IV infusion is administered by a healthcare professional over a period of no less than 15 minutes.

- An infusion administered once every 2 years is now approved in the United States for **prevention** of osteoporosis in postmenopausal women.

Bisphosphonates (cont'd)

***Efficacy*.**

- Of the antiresorptive agents, provide the **greatest fracture risk reductions & BMD ↑**
- BMD ↑ with bisphosphonates are dose dependent & greatest in the first 6-12 months of therapy
- because of a lack of fracture data in men, bisphosphonates are only FDA indicated to ↑ BMD, not to ↓ fracture risk in men

Long term efficacy of bisphosphonates

- While current treatment guidelines offer recommendations on when to start bisphosphonate therapy, the optimal length of bisphosphonate therapy remains unclear.

- Several clinical studies have shown that up to **ten years** of alendronate therapy is associated with sustained increases in BMD and appear to cause no harm.

Bisphosphonates (cont'd)

- In the only study to compare continuing a bisphosphonate compared with stopping it, the **F**racture Intervention Trial **L**ong-term **Ex**tension (FLEX) trial found that taking alendronate longer than five years does not provide much additional protection against fractures.

- In this trial, women who discontinued alendronate **after five years had a moderate decline in bone mineral density (BMD) and a gradual increase in serum markers of bone turnover compared with women who continued taking alendronate for an additional five years**. However, the mean BMD levels among patients who discontinued therapy remained at or above baseline levels which were measured ten years earlier.

Bisphosphonates (cont'd)

- Similar sustained beneficial effects of long-term (up to five years) treatment with risedronate have been demonstrated.

- However, there is no information regarding the other oral bisphosphonates to support the sustained duration of action after discontinuation.

Bisphosphonates (cont'd)

Adverse Events/Precautions.

- GI ADRs are minimal if the medication is taken correctly
  - weekly & monthly therapies have similar common but less-serious GI effects (perforation, ulceration, GI bleeding) than daily therapy.
  - GI event rates were **not** ↑ with concomitant NSAID use
  - IV ibandronate & zoledronic acid can be used for patients with c/i or intolerances to oral Bisphosphonates
- the most common ADRs of IV Bisphosphonates : fever, flu-like symptoms, & local injection-site reactions
- rare ADR: osteonecrosis of the jaw
  - routine dental care & good oral hygiene should be encouraged in anyone beginning Bisphosphonates therapy.
  - major dental work probably should be completed prior to beginning Bisphosphonates if possible

Osteonecrosis of the jaw

- Osteonecrosis of the jaw is a rare but serious disorder. Jaw osteonecrosis is very difficult to treat, often requiring multiple surgeries and courses of antibiotics.
- The surgeries often cause disfigurement, and areas of necrosis may not heal. Before its association with BPs, osteonecrosis of the jaw was most often seen in cancer patients who had radiation to the head and neck as part of their treatment.
- The exact mechanism is not fully understood. Patients who receive high-dose IV BPs for greater than two years are most at risk for developing osteonecrosis of the jaw. The estimated osteonecrosis risk ranges from 0.8% to 20% in these patients.
- It seems that the higher the BP dose and the longer the exposure time, the more likely the chance that osteonecrosis of the jaw will develop.

Bisphosphonates and Increased Fracture Risk

- BP inhibit an enzyme necessary for formation of the cytoskeleton in osteoclasts thereby strongly inhibiting bone resorption. The estimated half-life of BP is greater than 10 years once they are incorporated into mineralized bone.
- It is postulated that when bone containing BP is resorbed, some of the BP released is ***recirculated and binds again to bone surfaces to inhibit bone resorption.*** However, long-term suppression on bone remodeling can be detrimental. One purpose of bone remodeling is to refresh the bone and to repair the microscopic damage that accumulates within any structure. There is increasing evidence to suggest that long-term BP use ***may overly suppress bone metabolism***, limiting repair of micro damage and potentially increasing the risk for fractures in some patients.
- **In a report conducted by the American Society for Bone and Mineral Research in 2010,286 cases of atypical fractures in patients taking BP therapy for osteoporosis were identified. Investigators determined that atypical fractures of the subtrochanteric and femoral shaft more often occurred in patients treated with long-term (1.3 to 17 years, median seven years) BP.**

Comments on the risk of atypical fractures with bisphosphonates:

- Although there appears to be an association of fractures, it is **not known** if bisphosphonates are the cause of the fractures.
- In general, patients with osteoporosis are more likely to fracture bones. Furthermore, other studies have found no association between bisphosphonates and atypical fractures. In addition, the incidence of atypical fractures is miniscule in comparison to the incidence of hip fractures due to osteoporosis.

Esophageal Cancer and Bisphosphonates

- Oral bisphosphonates can cause esophageal irritation and injury.
- Risk is reduced if **patients drink water and remain upright after administration**. Case reports of esophageal cancer after bisphosphonate use triggered additional study of cancer risk.

- For now, there is not enough information to link bisphosphonates and esophageal cancer.

Mixed Estrogen Agonists/Antagonists (EAAs)

- **Raloxifene**, a second generation (EAA)
- approved for prevention & treatment of postmenopausal osteoporosis
- estrogen agonist on bone but antagonist on the breast & uterus

Efficacy.

- ↓vertebral fractures & ↑ spine & hip BMD, but to a lesser extent than bisphosphonates
- after discontinuation, the effect is lost
- has an FDA-approved indication for invasive breast cancer risk reduction → **dual osteoporosis & breast cancer prevention**
- some positive lipid effects (↓ total & LDL, neutral effect on HDL, slightly ↑ TGs);
- but no ↓ in cardiovascular effects was demonstrated

EAAs (cont'd)

Adverse Events/Precautions.

- hot flushes
- rarely endometrial bleeding
- contraindicated in active or past history of venous thromboembolic event
- should be stopped if a patient anticipates extended immobility
- slight ↑ in fatal stroke → women at high risk for a stroke or coronary events & those with known CAD, PVD, AF, or a prior history of CVA might not be good candidates for this medication

Administration.

- adherence & persistence problems exist

Calcitonin

- is released from the thyroid when SrCa is ↑
- **Salmon calcitonin** is > potent & longer lasting than the mammalian FDA indicated for osteoporosis treatment for women who are at least 5 years past menopause
- not approved for men & concomitantly with glucocorticoids
- ***is reserved as 3rd-line treatment***

Efficacy.

- only vertebral fractures ↓ with intranasal calcitonin
- does not consistently affect hip BMD & does not ↓hip fracture risk
- might **provide pain relief** to some pts. with acute vertebral fractures
- should be prescribed for short-term (4 weeks)
- should not be used in place of other > effective & < expensive analgesics or more appropriate osteoporosis therapy

Estrogen Therapy

- FDA indicated for prevention of osteoporosis,
- should **only be used short-term** in women who need estrogen therapy for the management of menopausal symptoms such as hot flushes.
- **risks of estrogen therapy outweigh the bone benefits**
- Estrogen with (HT) or without (ET) progestin therapy significantly ↓ fracture risk
- ↑ in BMD are < than bisphosphonates or teriparatide,but > than raloxifene & calcitonin
- **oral & transdermal** estrogens at equivalent doses & **continuous or cyclic** HT regimens have similar BMD effects
- fracture risk ↓ has not been demonstrated with lower dose therapy
- when ET or HT is discontinued, bone loss accelerates & fracture protection is lost
- the lowest effective dose should still be used for preventing & controlling menopausal symptoms with use discontinued with symptom abatement

Testosterone

- ↓ testosterone concentrations are seen with certain gonadal diseases, eating disorders, glucocorticoid therapy, oophorectomy, menopause, & andropause
- testosterone replacement is not approved for the prevention or treatment of osteoporosis
- *should **not be used solely** for the prevention or treatment of osteoporosis, but might be beneficial to ↓ bone loss in patients needing therapy for hypogonadal symptoms*
- Patients should be evaluated within 1-2 months of initiation & then every 3-6 months thereafter
- testosterone & methyltestosterone are in **pregnancy category X**
- testosterone products are **schedule III drugs**
- gel products can rub off & be absorbed by the patient's partner

Thiazide Diuretics

- Thiazide diuretics increase urinary calcium reabsorption.
- Observational studies suggest that patients who receive thiazide diuretics have a greater bone mass, lower rates of bone loss, and fewer fractures.
- Two prospective, controlled trials demonstrated small increases in bone mass over placebo.
- **Prescribing thiazide diuretics solely for osteoporosis is not recommended but is a reasonable choice for the patient with osteoporosis who requires a diuretic and for patients on glucocorticoids with greater than 300 mg of calcium excreted in the urine over 24 hours.**

Anabolic Therapies

Teriparatide

- is the only available medication that ↑ **bone formation**
- is a recombinant product representing the first 34 amino acids in human PTH
- both bone mass & architecture are improved
- FDA indicated for postmenopausal women & men who are at high risk for fracture
- Pts. who have a history of osteoporotic fracture, multiple risk factors for fracture, very low bone density **(e.g., T-score < –3.5),** or have failed or are intolerant of previous bisphosphonate therapy are candidates for PTH therapy
- discontinuation of therapy results in ↓ in BMD, although some anti-fracture efficacy appears to be maintained

Teriparatide

- Teriparatide is approved only for duration **of two years.**

- A gradual decrease in bone mass has been noted after discontinuation of teriparatide therapy;however, following therapy with a bisphosphonate has been shown to preserve the benefits

RANK Ligand (RANKL) Inhibitor/Human Monoclonal Antibody

- **Denosumab** is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor approved by the FDA in 2010 for treatment of postmenopausal osteoporosis with a high risk of fracture.
- Denosumab inhibits theformation, function and survival of osteoclasts by binding to RANKL resulting in decreased bone resorption and increased bone mass and strength.
- Denosumab **(Prolia® 60 mg)** is administered SC every six months by a health professional. In addition calcium 1,000 mg and at minimum 400 IU of vitamin D must be taken daily.The reduced frequency and supervised administration of denosumab may help improve patient compliance.
- Pre-existing hypocalcemia must be corrected prior to initiating therapy.

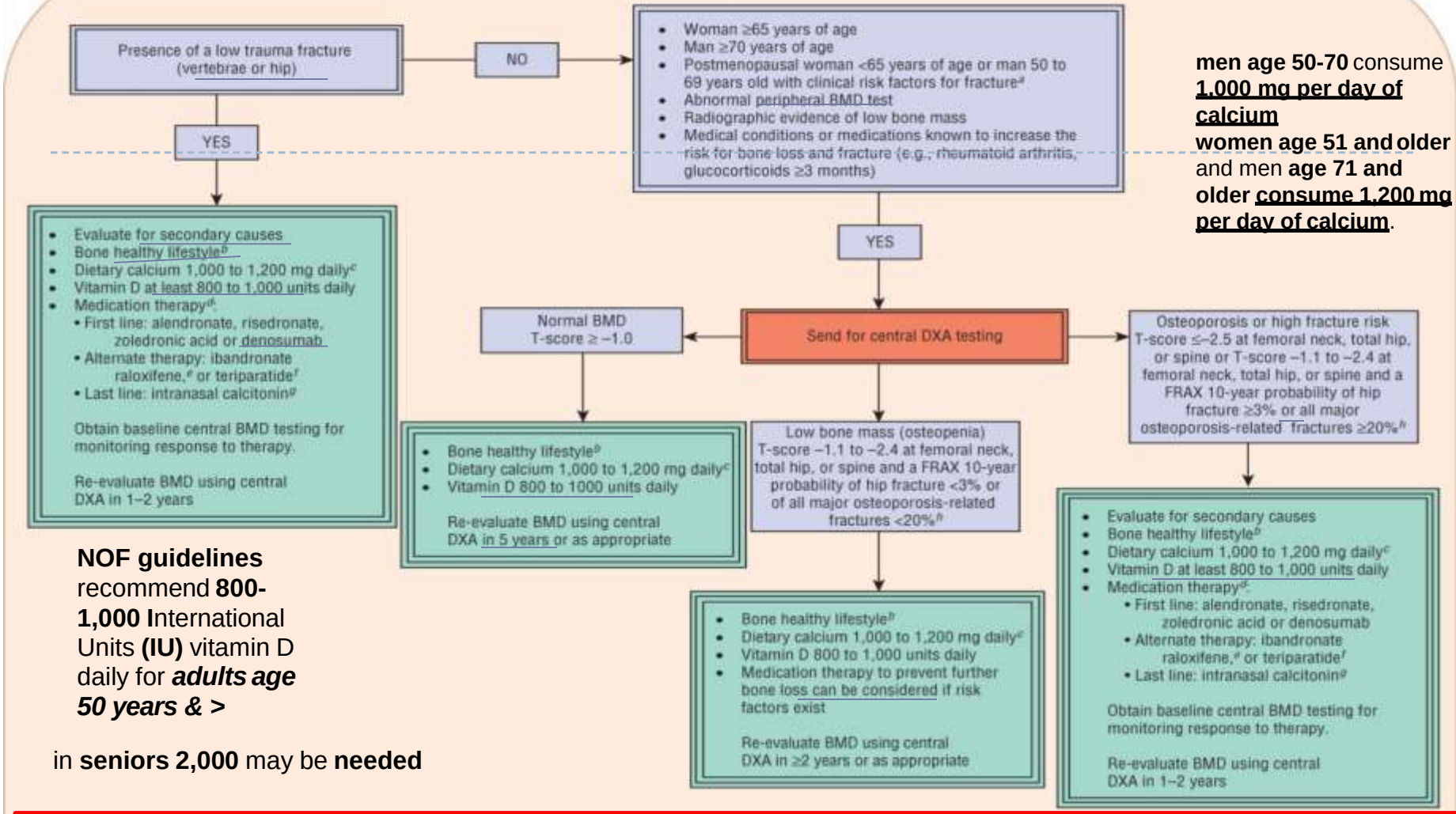
- **Xgeva® 120 mg (hypercalcemia of malignancy)**

Emerging therapies/Sclerostin inhibitors

- **Sclerostin inhibitors** – Sclerostin is produced by osteocytes and **inhibits bone formation**
- inhibition of sclerostin should enhance osteoblast function and improve bone mass
- a phase II trial in postmenopausal women, all doses of a monoclonal anti-sclerostin antibody (**romosozumab**) increased bone density at the LS, total hip, and femoral neck

Combination therapies

Combining potent antiresorptive agents results in small additional increments in bone density. In postmenopausal women (mean age, 61-62 y) with low bone mass,BMD improvements in the spine and hip with combined alendronate and ET were significantly greater (8.3%) than results for either agent alone (6.0%). Combined risedronate and ET/ EPT also has shown favorable, although modest, BMD effects compared with either agent alone. Whether increases in BMD result in better fracture protection is not known, and the long-term safety of combination therapies has not been evaluated.



men age 50-70 consume **1,000 mg per day of calcium**
women age 51 and older and men **age 71 and older consume 1,200 mg per day of calcium**.

NOF guidelines recommend **800-1,000 I**nternational Units **(IU)** vitamin D daily for ***adults age 50 years & >***

in **seniors 2,000** may be **needed**

[a]Major clinical risk factors for fracture: current smoker, low body weight or body mass index, history of osteoporosis/low trauma fracture in a first-degree relative, personal history of fracture as an adult (after age 50 years), excessive alcohol intake
[b]Bone-healthy lifestyle includes smoking cessation, limit alcohol intake, well-balanced diet with adequate calcium and vitamin D intakes, weight-bearing/resistance exercises, and fall prevention
[c]Dietary calcium preferred. If diet is inadequate, supplement as necessary
[d]Sometimes men with hypogonadism also receive testosterone replacement; sometimes women with menopausal symptoms receive low dose hormone therapy for a short time
[e]Raloxifene can be a good option in women at high risk for breast cancer
[f]Teriparatide can be considered a first-line option in patients with a very high risk of fracture (e.g., T-score <−3.5 or multiple low trauma fractures) or intolerant to other medications
[g]Calitonin is last-line due to limited fracture data and a recent concern over possible slight increased cancer risk.
[h]WHO absolute fracture risk assessment tool (FRAX) for osteoporotic fracture risk estimations

All therapies should be given with calcium and vitamin D supplementation.

men age 50-70 consume **1,000 mg per day of calcium**
women age 51 and older and men **age 71 and older consume 1,200 mg per day of calcium**.

[a]Major clinical risk factors for fracture: current smoker, low body weight or body mass index, history of osteoporosis/low trauma fracture in a first-degree relative, personal history of fracture as an adult (after age 50 years), excessive alcohol intake
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Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM:
Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:
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Management

- **Initial therapy** — For most postmenopausal women with osteoporosis, we suggest oral bPs as first-line therapy. (efficacy, favorable cost, and the availability of long-term safety data).
- We suggest alendronate or risedronate as our choice of bPdue to efficacy in reducing vertebral and hip fracture.
- For patients with severe osteoporosis (T-score of -3.5 or below even in the absence of fractures, or T-score of -2.5 or below plus a fragility fracture), initial treatment with teriparatide is an alternative. Because treatment with teriparatide is limited to 24 months, patients with severe osteoporosis who are treated with teriparatide first are typically treated with an antiresorptive agent (eg, bPs) after discontinuing teriparatide.

Contraindications/intolerance to oral bisphosphonates

- Oral bPs should not be used as initial therapy in patients with esophageal disorders, an inability to follow the dosing requirements (e.g., stay upright for at least 30 to 60 minutes), or CKD : [eGFR] rate <30 mL/min
- Oral bPs should also be avoided after certain types of bariatric surgery in which surgical anastomoses are present in the GI tract.
- Alternatives for initial therapy in patients with contraindications or intolerance to oral bPs include IV bPs (except if the contraindication is CKD), denosumab, teriparatide (except in CKD), and selective estrogen receptor modulators (SERMs).
- The choice of initial agent depends upon the nature of the contraindication/intolerance, the severity of the osteoporosis, and subsequent risk for fracture.

Contraindications/intolerance to oral bisphosphonates

- Among IV bPs.: We prefer **IV** zoledronic acid, which has been demonstrated to reduce **vertebral and hip fractures**. IV ibandronate is also available; however, there is as yet no direct fracture prevention data for IV ibandronate.
- Denosumab **is an alternative to IV** zoledronic acid **for women at high risk for fracture (such as older patients) who have difficulty with the dosing requirements of oral bPs**, who prefer to avoid IV bPs due to side effects (eg, acute phase reaction), or who have impaired renal function.
- Teriparatide is rarely used as initial therapy, but it could be prescribed as an alternative to IV zoledronic acid for postmenopausal women with **severe** osteoporosis (T-score of -3.5 or below even in the absence of fractures, or T-score of -2.5 or below plus a fragility fracture) who were treated initially with oral bPs but who are unable to tolerate them.

Response to therapy

- **Decline in BMD**
- When the change in BMD is <5 % and the patient is taking the drug correctly and has no discernible contributing factors, we suggest continuing the same therapy and repeating the BMD two years later.
- •When the decline in BMD is ≥5 %, we usually switch from an oral bP to an IV bP, typically zoledronic acid. If the lack of response is related to poor absorption, switching to an IV preparation should result in a more favorable response. Other alternatives include switching to denosumab or teriparatide.

Response to therapy

- ●**Fracture while taking bPs** – Switching to teriparatide is a good option for patients with severe osteoporosis (T-score <-2.5 and at least one fragility fracture) who continue to fracture after one year of bisphosphonates. Teriparatide is effective in increasing BMD in women previously treated with bisphosphonates, although the improvement may be less than in women not previously exposed to bPs.
- Denosumab is an alternative for patients who are unresponsive to other therapies and in those with impaired renal function. However, if there are no contraindications, it may be beneficial to treat with teriparatide first (maximum of two years), followed by denosumab, to preserve the gains in BMD achieved with teriparatide.

Medication	Indications	Reduction in Fracture Risk[2]	Adverse Drug Reactions[1]	Contraindications
Bisphosphonates				
Alendronate	**TREATMENT** • Postmenopausal osteoporosis • Increase bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women **PREVENTION** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia, flu-like symptoms (rare postmarket experience) • Atypical fracture of the thigh	• Abnormalities of the esophagus that delay esophageal emptying • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with CrCl ≤ 35 ml/min
Ibandronate	**TREATMENT** • Postmenopausal osteoporosis **PREVENTION** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: + Hip: -	• Esophagitis, abdominal pain, diarrhea • Influenza-like illness, jaw osteonecrosis (rare) musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia • Atypical fracture of the thigh	• Uncorrected hypocalcemia • Inability to stand or sit upright at least 60 minutes • Hypersensitivity • Not recommended for patients with CrCl ≤ 30 ml/min

Medication	Indications	Reduction in Fracture Risk[2]	Adverse Drug Reactions[1]	Contraindications
Risedronate	**TREATMENT** • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis • Increase bone mass in men with osteoporosis **PREVENTION** • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia • Atypical fracture of the thigh	• Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with CrCl ≤ 30 ml/min
Risedronate delayed release	**TREATMENT** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia • Atypical fracture of the thigh	• Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with CrCl ≤ 30 ml/min
Zoledronic acid	**TREATMENT** • Postmenopausal osteoporosis • Paget's disease	Vertebral: +++ Non-vertebral: ++ Hip: ++	• Acute phase reaction: fever, flu-like symptoms, HA, arthralgia/myalgia • Jaw osteonecrosis (rare), transient increase in creatinine, atrial fibrillation, hypocalcemia • Atypical fracture of the thigh	• Hypersensitivity to zoledronic acid or any of its excipients • Uncorrected hypocalcemia • Not recommended in patients with a creatinine clearance less than 35 mL/min

Medication	Indications	Reduction in Fracture Risk[2]	Adverse Drug Reactions[1]	Contraindications
Selective Estrogen Receptor Modulator (SERM)				
Raloxifene (Evista®)*	**TREATMENT** • Postmenopausal osteoporosis **PREVENTION** • Postmenopausal osteoporosis	Vertebral: +++ women without fx ++ women with fx Non-vertebral: - Hip: -	• Hot flashes • Leg cramps • Increased risk of venous thromboembolic events	• Pregnancy • History of venous thromboembolism • Hypersensitivity • Nursing women
Parathyroid Hormone (PTH)				
Teriparatide	**TREATMENT** • Postmenopausal osteoporosis with high risk for fracture (history of osteoporotic fracture, multiple risk factors, failed/intolerant of previous therapy) • Glucocorticoid-induced osteoporosis with high risk of fractures • Increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture (history of osteoporotic fracture, multiple risk factors, failed/intolerant of previous therapy)	Vertebral: +++ Non-vertebral: +++ Hip: N/A	**BLACK BOX WARNING:** shown to cause an increase in the incidence of osteosarcoma in male and female rats, dependant on dose and duration of treatment. • Orthostatic hypotension • Increase in serum calcium • Increase in urinary calcium • Increase in serum uric acid	• Paget's disease • Any prior therapeutic radiation involving the skeleton • Bone metastases or history of skeletal malignancies • Metabolic bone disease (other than osteoporosis) • Hypercalcemia • Pregnant and nursing women • Unexplained elevated alkaline phosphatase • Hypersensitivity, pediatric populations or young adults with open epiphyses
Calcitonin				
Calcitonin-salmon (Miacalcin® and Fortical® nasal spray)	**TREATMENT** • Postmenopausal osteoporosis in women with at least five years postmenopause with low bone masss relative to healthy premenopausal females	Vertebral: + Non-vertebral: - Hip: -	• Nausea • Flushing • Rhinitis with nasal spray	• Hypersensitivity