



Diagnosis and management of osteoporosis- can we make it simple?

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Definition of osteoporosis



Disease definition



Healthy bone

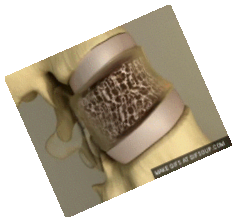


Osteoporotic bone

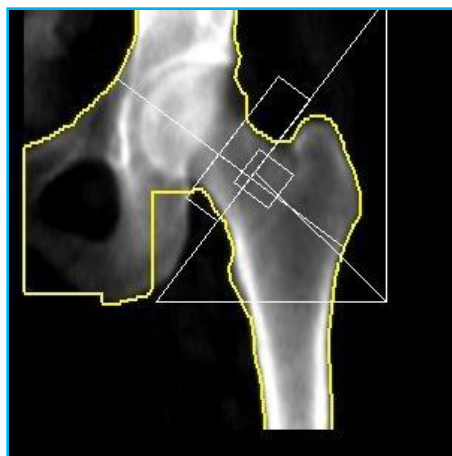
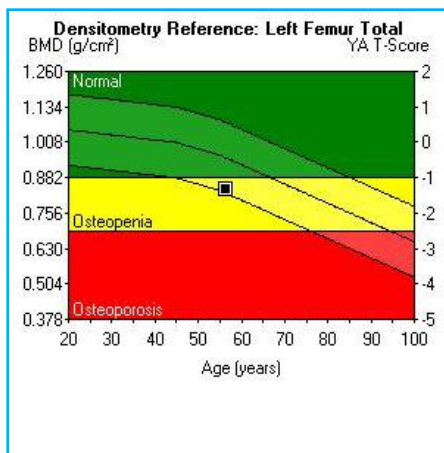
- low bone mass,
- deterioration of bone tissue,
- disruption of bone microarchitecture
- increase in the risk of fragile fractures

NIH, JAMA. 2001;285:785-795.

Sözen et al. Osteoporosis. Eur J Rheumatol 2017; 4: 46-56.
Indian Journal of Clinical Practice, Vol. 23, No. 12, May 2013.



WHO Definition of Osteoporosis:

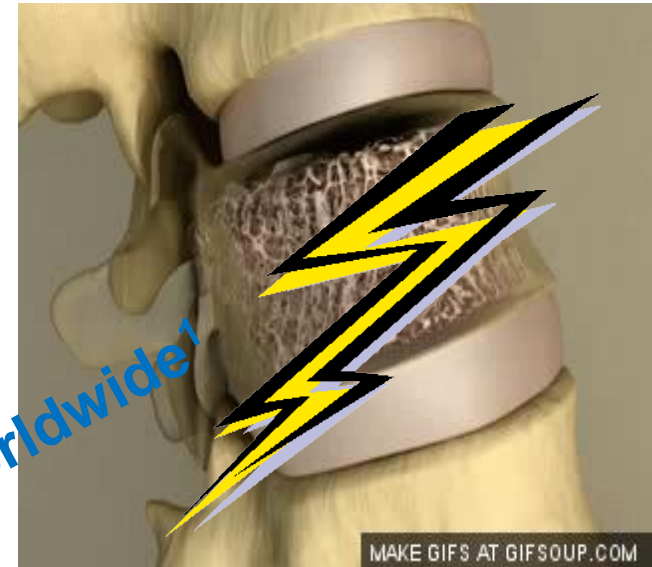


DEFINITION BY DXA SCORING

T score	Category
≥ -1	Normal
< -1 to ≥ -2.5	Osteopenia
< -2.5	Osteoporosis
< -2.5 with fragility fracture	Established/severe osteoporosis

Incidence & Epidemiology

- Osteoporosis is a global major health problem.
- Worldwide, osteoporosis causes more than **8.9 million fractures** annually^{1,2}
- Osteoporosis affects an estimated 75 million people in Europe, USA and Japan,^{1,2,3} 2.2 million in Australia^{2,4} and 70 million in China^{2,5}
- Diagnosis and treatment increased in Western countries, however, less attention is given in the Middle East and African countries⁶



**Every 3 seconds
an osteoporotic
fracture occurs^{1,2}**

¹Johnell O, et al. Osteoporos Int. 2006;17:1726.

²<https://www.iofbonehealth.org/facts-statistics#category-14>

³EFFO and NOF 1997, Osteop Int. 7:1

⁴Sambrook PN, et al. Med J Aust 176 Suppl:S1.

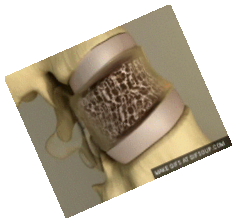
⁵China Health Promotion Foundation 2008

⁶Vijayakumar R, et al. Journal of Local and Global Health Science 2016:2

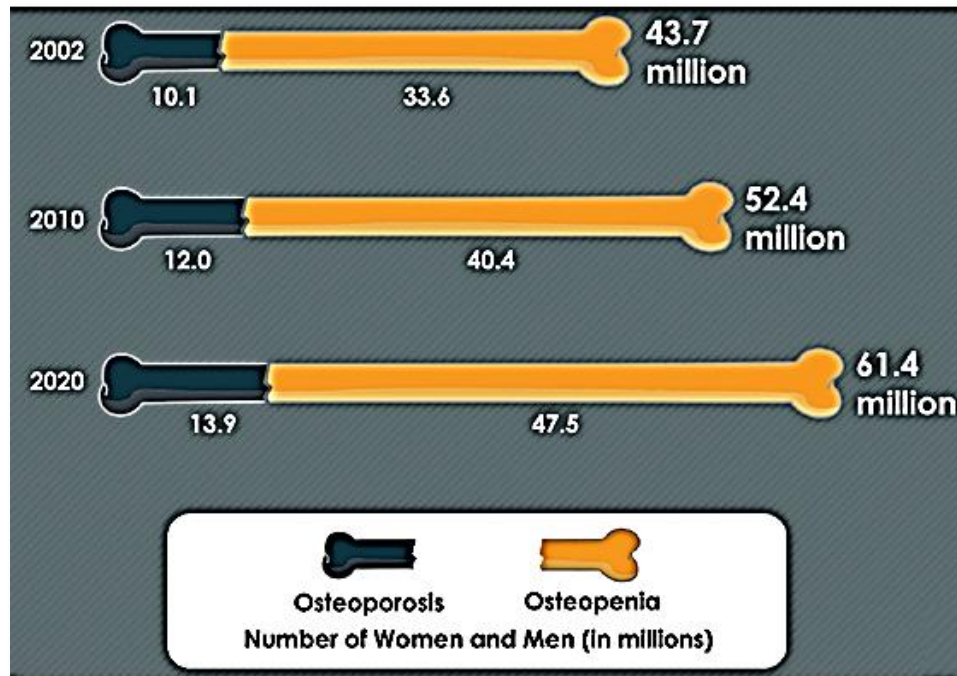
EFFO European Foundation for Osteoporosis

NOF National Osteoporosis Foundation

¹Kanis JA (2007) WHO Technical Report, University of Sheffield, UK

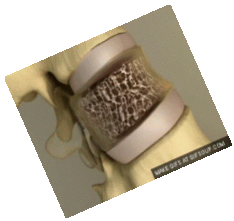


Osteoporosis prevalence



Projected growth in the US prevalence of osteopenia and osteoporosis. Data from the National Osteoporosis Foundation

The prevalence of osteopenia and osteoporosis is estimated to increase by another **9 million individuals from 2010 to 2020**



OP in special situations:

Glucocorticoid Induced OP-

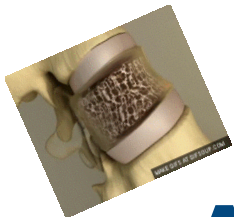
- 50% patients with long term therapy.
- Most rapid loss in first 6-12 month
- Overall prevalence of vertebral fracture is 28%.

■ HIV AIDS &OP

- patients are at high risk for early OP due to multiple causes.
- 15% of HIV patients have OP
- 3.68 times more prone to OP than normal counterpart.

■ 4 types- OP in pregnancy:

- Idiopathic OP
- Transient OP of hip.
- Post pregnancy spinal OP
- Lactation associated OP.



Asian study

- By 2050 more than 50% of all osteoporotic fracture will occur in Asia.

Facts About Osteoporosis



Around the world, at least one in three women and one in five men over the age of 50 will suffer a fracture caused by weak bones.



Fractures result in pain, debilitation and loss of quality of life.



Thirty-three per cent of older adults who suffer a hip fracture become physically impaired and lose their ability to live independently one year after the fracture.



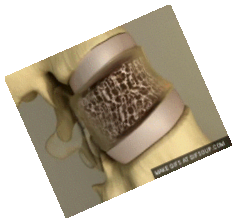
At least one in five will die within the year following fracture.



Vertebral (spine) fractures can cause extreme pain, long or short term disability, dowager's hump, and significant loss in quality of life.



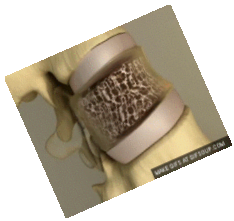
Without treatment, the risk of suffering a cascade of new fractures is very high.



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Mortality & Morbidity:

- Hip fractures result in a 10% to 20% > mortality risk within 1 year.
- Hip fracture vs breast cancer – 2.8%.
- 55% more co-morbidity like pneumonia,

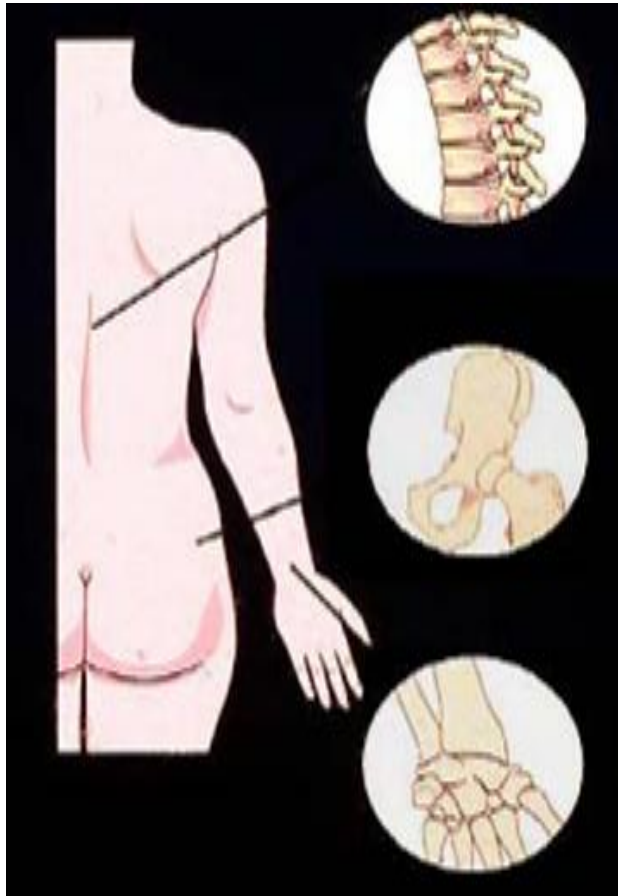


Osteoporotic fractures - fragility fractures, low-trauma fractures



Clinical manifestations

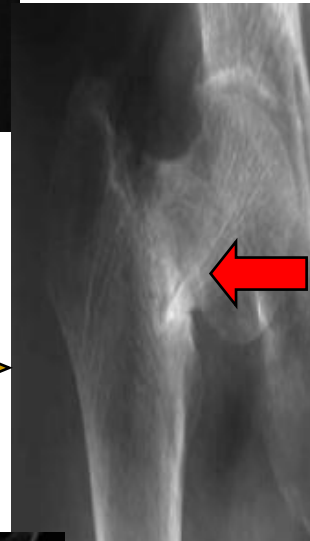
Common Fracture Sites



Spine



Hip

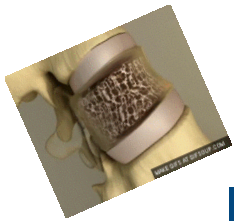


Wrist



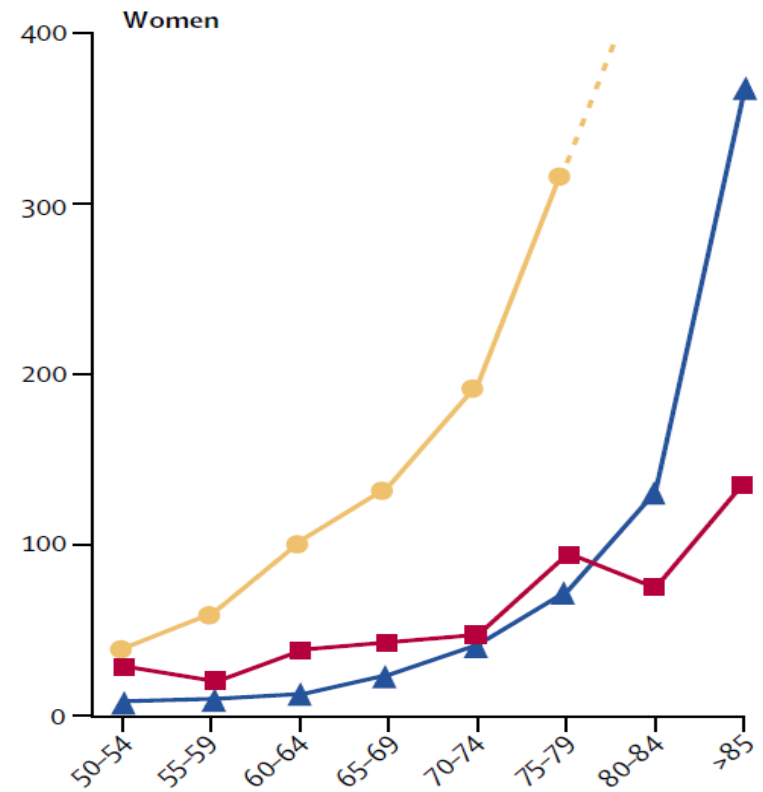
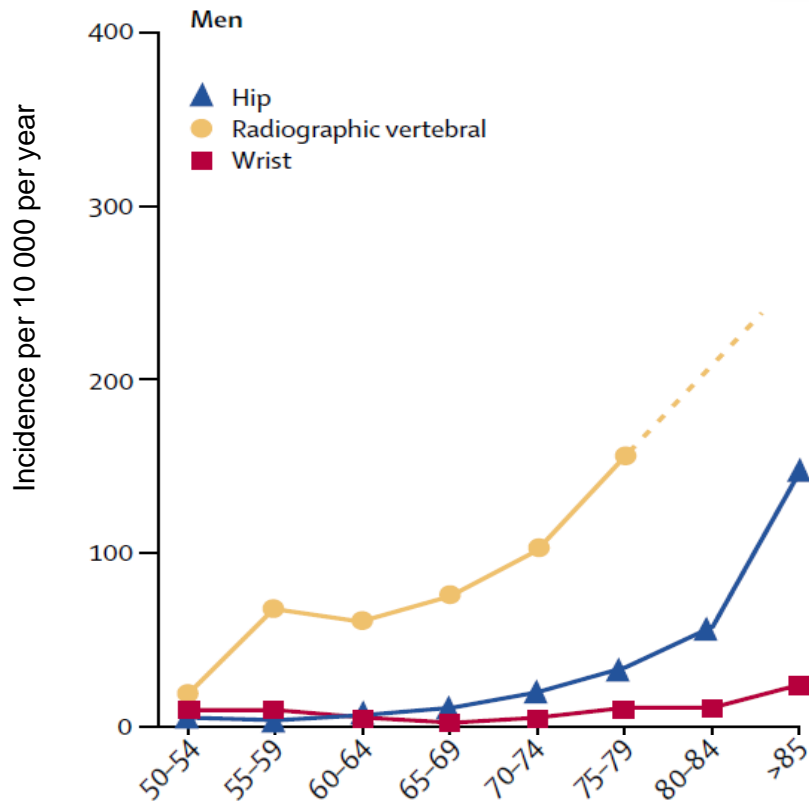
Uncommon sites

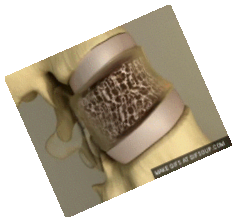
- Humerus, Ribs, Tibia, Pelvis



Incidence of osteoporotic fracture

Age-specific and sex-specific incidence of radiographic vertebral, hip, and distal forearm fractures





Diagnosing of osteoporosis



Procedures proposed in the investigation of osteoporosis

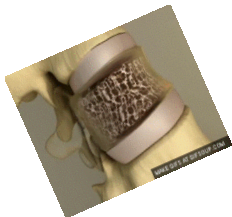
Routine

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein. Serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- Thyroid function tests
- Bone densitometry (DXA)

Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine or DXA-based lateral vertebral imaging
- Serum protein immunoelectrophoresis and urinary Bence Jones proteins
- Serum 25-hydroxyvitamin D
- Plasma parathyroid hormone
- Serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone
- Serum prolactin
- 24 hour urinary free cortisol/overnight dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies
- Isotope bone scan
- Markers of bone turnover
- Urinary calcium excretion

Other investigations, for example, bone biopsy and genetic testing for osteogenesis imperfecta, are largely restricted to specialist centres.

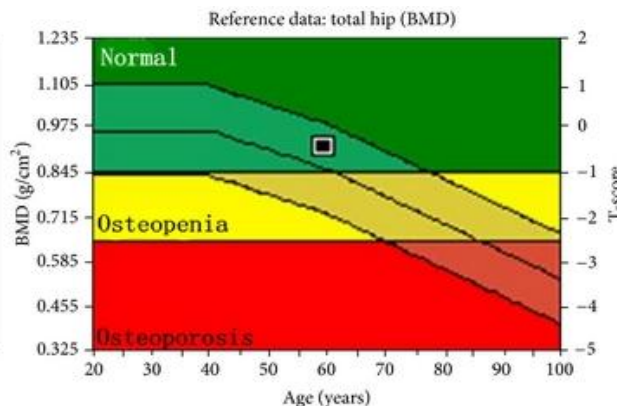


Diagnosis of osteoporosis

Osteoporosis is defined by the WHO as a value for BMD 2.5 standard deviations or more below the healthy young adult mean (**T-score of -2.5**), where a T-score of zero is equal to the young adult mean^{1,2}

BMD is typically measured using DXA^{1–3}

- Low radiation X-rays detect small amounts of bone loss
- Measures spine and hip bone density, and also bone density of the whole skeleton



BMD and fracture risk should be assessed in:

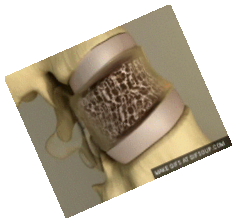
- **women** aged over 65 years or 50–64 with certain risk factors⁴
- **Men** aged over 70 years or 50–69 with certain risk factors⁵
- patients receiving any dose of **glucocorticoid** for at least 3 months^{6,7}

Fracture risk assessment is also performed using **FRAX®**, which calculates the **10-year probability of major fracture by integrating several risk factors**^{1,2,8}

¹Hernlund E, et al. Arch Osteoporos 2013;8:136. ²Kanis JA, et al. Osteoporos Int 2013;24(1):23–57. ³Das S, et al. Drug Des Devel Ther 2013;7:435–448.

⁴O'Connor KM. Med Clin North Am 2016;100(4):807–826. ⁵Watts NB, et al. J Clin Endocrinol Metab 2012;97(6):1802–1822. ⁶Briot K, et al. RMD Open 2015;1. ⁷Grossman JM, et al. Arthritis Care Res (Hoboken) 2010;62(11):1515–1526. ⁸Curtis EM, et al. Clin Med (Lond) 2015;15(Suppl 6):s92–s96.

⁹Small RE. MedGenMed 2005;7(2):3. Image: <https://www.hindawi.com/journals/ije/2013/895474/fig2/> Clinician's Guide to prevention & treatment of osteoporosis ,2014,Ver:01. National Osteoporosis Foundation(USA)



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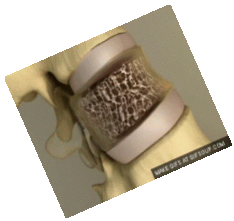


Dual energy x-ray absorptiometry

DEXA is the “gold standard”

- **Advantage:**

- Non-invasive
- Involves no special preparation
- Radiation exposure is minimal (1-4 uSV)
- The procedure is rapid, only takes about 20 minutes

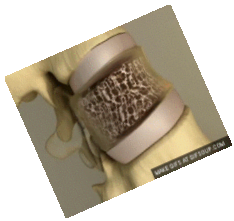


Contd....

Screening- Ultrasound Densitometry

- **Advantage**
 - Can predict fracture risk in the elderly
 - Relatively inexpensive, portable
 - Uses no radiation
- **Disadvantage-**
 - can be used only in peripheral sites (eg. calcaneus, wrist), where bone is relatively superficial.



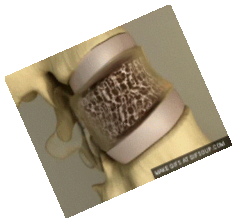


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BMD Test Methods

- Quantitative computerized tomography (QCT)
- Quantitative ultrasound (QUS)
- Peripheral dual energy X-ray absorptiometry (pDEXA)
- Radiographic absorptiometry (RA)

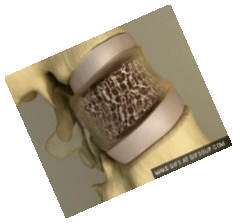


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Alveolar Gray Scale- Pixel Intensity of Mandible

- Pixel intensity in mandible may be another easy tool for assessing BMD.
- Changes in MABM were strongly correlated with the BMD.
- This combined relationship can be used as an easy diagnosis tool for OP.



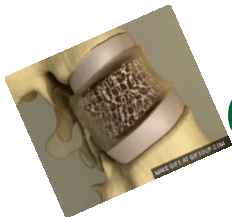
Contd....



Diagnosis

FRAX

- Developed in 2008 by WHO.
- Applicable aged 40-90 years.
- Outputs are 10 year probability of hip fracture and a major fracture- vertebral.
- Can be used with or without BMD results.
- To decide treatment in osteoporosis.



Contd....



FRAX Tool: On-line Calculator

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: **Canada**

Name/ID:

[About the risk factors](#)

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age:

Date of birth:

Y: M: D:

2. Sex

☐ Male ☒ Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture

☒ No ☐ Yes

6. Parent fractured hip

☒ No ☐ Yes

7. Current smoking

☒ No ☐ Yes

8. Glucocorticoids

☒ No ☐ Yes

9. Rheumatoid arthritis

☒ No ☐ Yes

10. Secondary osteoporosis ☒ No ☐ Yes

11. Alcohol 3 or more units per day ☒ No ☐ Yes

12. Femoral neck BMD (g/cm²)

T-Score

BMI 23.4

The ten year probability of fracture (%)



with BMD

☒ Major osteoporotic

7.5

☒ Hip fracture

1.0

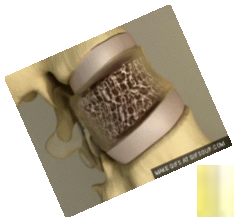


Weight Conversion

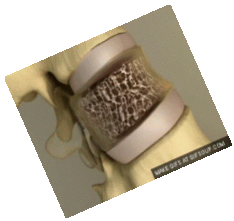
Pounds Kgs

Height Conversion

Inches Cms



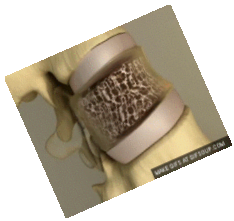
The FRAX calculator in 63 countries and in 34 languages including **Bengali**
FRAX online risk assessments reach **20 million milestone**.



TBS

Bone density + microarchitecture- L1-L4

- 1350 or above- Normal.
- 1350-1200- Osteopenia
- Less than 1250 - OP



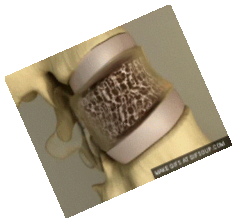
Treatment

Best approach

Intervention strategies based on fracture probabilities are highly effective, and more reliable than the use of BMD alone both in terms of identifying high-risk individuals for treatment and in avoiding intervention in those at low risk.

BMD & FRAX combination is better

**+ TBS- bone density + microarchitecture
1350-1200- <. ? Best.**

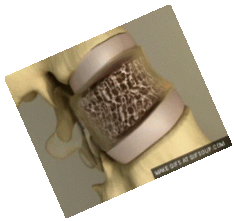


Diagnosis

Biochemical markers of bone turnover

Biochemical markers of bone remodeling [e.g. resorption markers-serum C-telopeptide (CTx) and urinary N-telopeptide (NTX) and formation markers-serum bone specific alkaline phosphatase (BSAP), osteocalcin (OC) and amino-terminal propeptide of type I procollagen (PINP)] are collected in the morning while the patient is fasting.

Biochemical markers of bone turnover determination for research, not clinical implications.

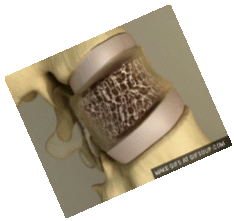


Treatment:



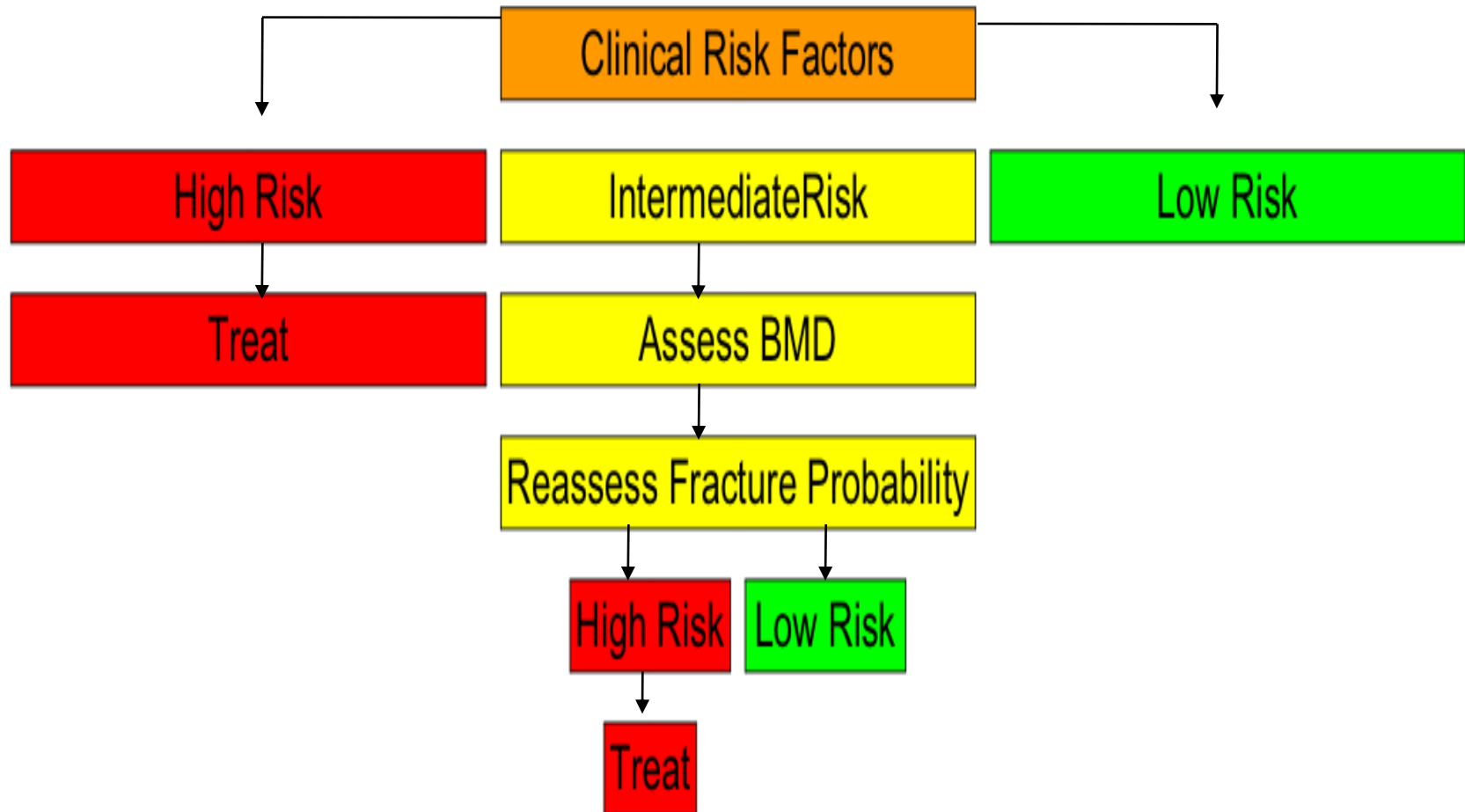
Goals of treatment

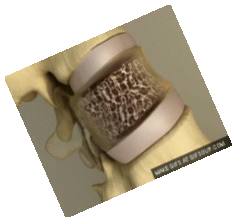
- Prevent further bone loss.
- Increase or at least stabilize bone density.
- Prevent further fractures.
- Relieve deformity (e.g., kyphoplasty)
- Relieve pain.
- Increase level of physical functioning.
- Increase quality of life.



Management

WHO Algorithm





Treatment Algorithm for Osteoporosis

AACE/ACE 2016 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5 , a history of fragility fracture, or high FRAX[®] fracture probability*

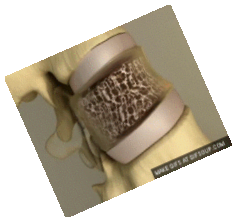
Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

No prior fragility fractures or moderate fracture risk**

Prior fragility fractures or indicators of higher fracture risk**



Treatment Algorithm for Osteoporosis (Contd...)



AACE/ACE 2016 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

- Alendronate, denosumab, risedronate, zoledronic acid***
- Alternate therapy: Ibandronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

- Denosumab, teriparatide, zoledronic acid***
- Alternate therapy: Alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Teriparatide for up to 2 years

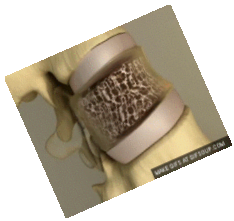
Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

- * 10 year major osteoporotic fracture risk $\geq 20\%$ or hip fracture risk $\geq 3\%$. Non-US countries/regions may have different thresholds.
- ** Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
- *** Medications are listed alphabetically.
- **** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.

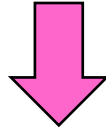




Management of Osteoporosis

Treatment / Secondary Prevention

Lifestyle



- ❑ Diet
- ❑ Exercise
- ❑ Smoking
- ❑ Alcohol Intake
- ❑ Sunlight Exposure

Pharmacological

- ❑ Drugs altering BMD
- ❑ Analgesia

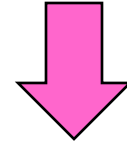
Non-pharmacological

- ❑ Physiotherapy
- ❑ Pain Relief

Falls Assessment

Prevention / Primary Prevention

Lifestyle



- ❑ Diet
- ❑ Exercise
- ❑ Smoking
- ❑ Alcohol Intake
- ❑ Sunlight Exposure

Pharmacological

- ❑ Drugs altering BMD

Non-pharmacological

- ❑ Physiotherapy
- ❑ Hip Protectors

Prevention of Falls

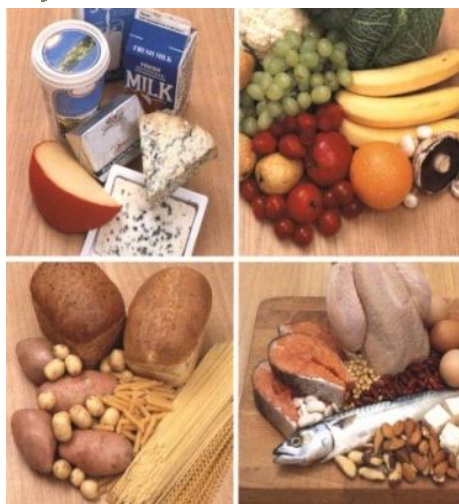
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Lifestyle Advice

Diet

Balanced diet. Calcium 1200 mg/day 800 to 1000 (IU) of vitamin D/day Amino acids Alanine, arginine.



Alcohol

Within safe limits
2u/day women
3u/day men



Exercise

Regular weight bearing exercise, muscle strengthening exercise 3 times a week for 20 minutes minimum



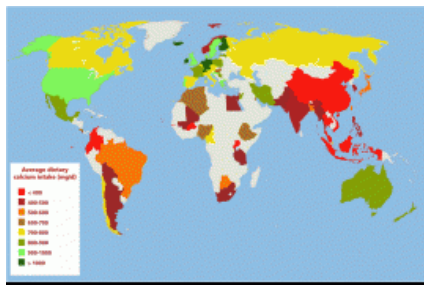
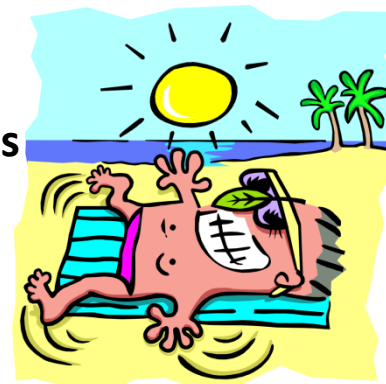
Smoking

Stop smoking



Sunlight Exposure

15-20 minutes on face, hands and forearms twice weekly form April to October



Nutr Rev 2008;66(suppl 2):5182-5194

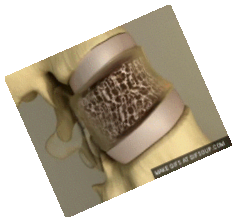
Endocr Pract 2009;15:95-103

Cangussu LM et al. Osteoporos Int 2015;26:2413-21

Wang J et al. J Bone Miner Res 2015;30:1641-50

Ann N Y Acad Sci 2006;1068:429-446

Clinician's Guide to prevention & treatment of osteoporosis ,2014,Ver:01. National Osteoporosis Foundation(USA Dr.Axe, Food is Medicine



Treatment of Osteoporosis...



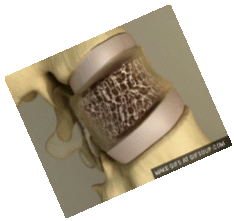
Role of Yogurt

A study published on May, 2017 led by Trinity College, Dublin, which was the largest observational study to date of dairy intakes and bone and frailty measurements in older adults has found that increased yogurt consumption was associated with a higher hip bone density and a significantly reduced risk of osteoporosis in older women and men on the island of Ireland.

- Total hip and femoral neck bone mineral density measures in females were 3.1-3.9% higher among those with the highest yogurt intakes compared to the lowest.
- In men, the biomarker of bone breakdown was 9.5% lower in those with the highest yogurt intakes compared to the lowest.

• a 31% lower risk of osteopenia and a 39% lower risk of OP in women.
• a 52% lower risk of OP in men.

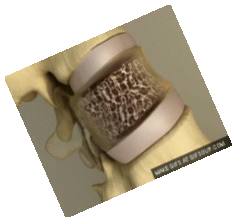




Regular Weight-Bearing and Muscle - Strengthening Exercise

- Muscle-strengthening exercise includes weight training and other resistive exercises, such as yoga, Pilates and boot camp programs.
- Weight-bearing exercise (in which bones and muscles work against gravity as the feet and legs bear the body's weight) includes ;
 - Walking
 - Jogging
 - Tai-chi
 - Stair climbing
 - Dancing
 - Tennis etc.

Weight-bearing exercise

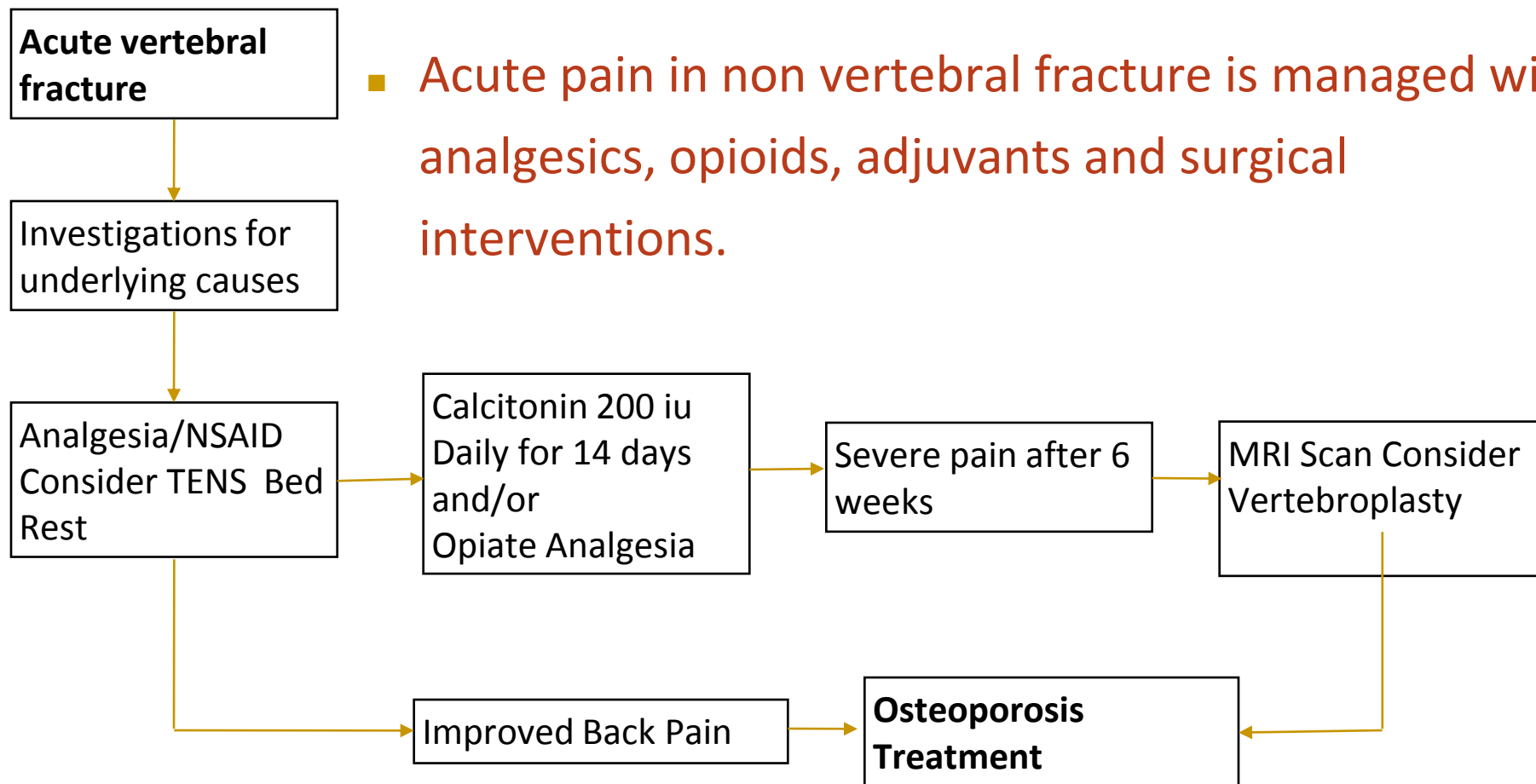


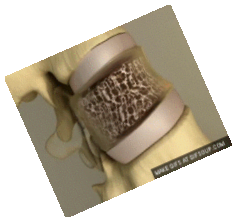
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Treatment of acute vertebral fracture pain

- Acute pain in non vertebral fracture is managed with analgesics, opioids, adjuvants and surgical interventions.



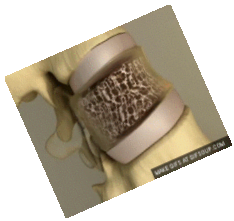


Medications Approved by the U.S. Food and Drug Administration for Osteoporosis



<i>Indication</i>	<i>Medication</i>	<i>Typical dosage</i>	<i>Route</i>	<i>Fracture type</i>
Prevention	Estrogen†, with or without progesterone	0.625 mg daily	Oral	Hip, vertebral, nonvertebral
Prevention and treatment	Alendronate (Fosamax)	70 mg weekly	Oral	Hip, vertebral, nonvertebral
	Ibandronate (Boniva)	150 mg monthly	Oral	Vertebral
	Risedronate (Actonel)	35 mg weekly	Oral	Hip, vertebral, nonvertebral
	Raloxifene (Evista)	60 mg daily	Oral	Vertebral
Treatment	Ibandronate	3 mg every three months for four doses	Intravenous	Increases bone mineral density, fracture end point not evaluated
	Zoledronic acid (Reclast)	5 mg annually for three doses	Intravenous	Hip, vertebral, nonvertebral
	Calcitonin (Miacalcin)	200 IU daily	Nasal	Vertebral
	Teriparatide (Forteo)	20 mcg daily up to two years	Subcutaneous	Vertebral, nonvertebral

All therapeutic management strategies for the prevention and treatment of osteoporosis include recommendations for **calcium and vitamin D supplementation**¹

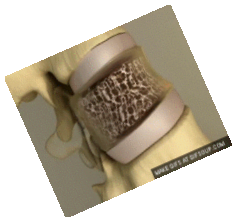


Bisphosphonates -

- **Alendronate**
- **Ibandronate**
- **Risedronate**
- **Zoledronic acid**

Anti-resorptive therapies such as bisphosphonates:

- reduce bone turnover
- inhibit further microarchitecture deterioration
- increase bone mass and quality
- strengthen bone
- reduce fracture risk



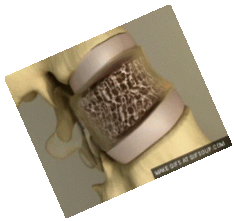
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Bisphosphonate should be used for at least 3 years, now extended treatment should be given.

	Treatment	Extended treatment
Alendronate study	0-4 years	5-10 years
Risedronate study	0-3 years	6-7 years
Zoledronic acid	0-3 years	4-6 years

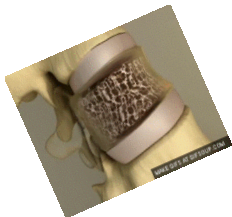
- Not at high fracture risk after 3-5 yrs of BP treatment, a drug holiday of 2-3 yrs can be considered.



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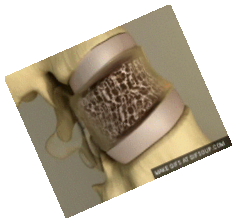
- Although IV BPs are generally safe, transient influenza-like symptoms.
- ONJ- 1-19 per 100,000 (IV: oral = 3:1).
- Cardiac arrhythmia- AF.
- Denosumab had lower ONJ.
- Atypical fracture of femur with BP for as long as 10 years – large studies – FIT, FLEX, HORIZON did not support



Mutation & bisphosphonates..

- A team of researchers of the University of Barcelona and the Hospital del Mar Medical Research Institute (IMIM) have discovered a new mutation is vulnerable to the bisphosphonate.
- Instead of strengthening the bone and prevent it from getting fractures, it worsens.

Some Controversies

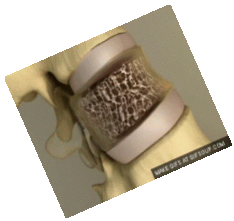


Other pharmacological options ...

- **Denosumab** is a fully humanised monoclonal antibody against Receptor Activator of Nuclear factor Kappa B Ligand (RANKL),
- **Raloxifene** is a selective oestrogen receptor modulator and inhibits bone resorption.
- **Teriparatide** - good anabolic activity and antiosteoporotic activity.

Abaloparatide is the first new anabolic treatment approved for postmenopausal OP

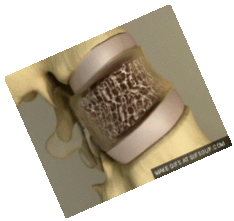
- in general, reductions of 30-70% have been reported for vertebral fracture, up to 20% for non-vertebral fracture and up to 40% for hip fracture.



Role of anabolic steroid:

Anabolic steroids exerts positive effects on vertebral BMD and on bone pain in postmenopausal OP.

Fracture reduction - needs prospective trials.



New pharmacological option...

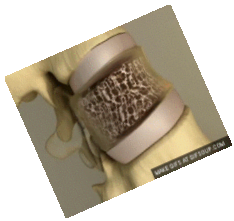
Icariin:

- Prenylated flavonol glycoside isolated from Epimedium herb-represent a class of flavonoids.
- Bone-promoting activity, which could be used as potential treatment of postmenopausal OP.



Novel & Future Therapies- new armaments

- Wnt protein modulating drugs
- Monoclonal antibody Sclerostin antagonist – Romosozumab.
- PTH & PTHrp analogues, possibly calcilytics- JTT305/MK-5442
- Inhibitors of bone resorption as Cathepsin K inhibitors- Odanacatib
- Sequential therapies with 2 or more bone active substances.
- Icariin!!!

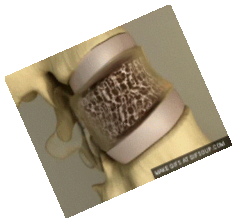


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Causes of Failure to Respond to OP Therapy

- Drug compliance
- Nutritional deficiency of Ca.
- Vitamin D deficiency
- Co-morbid condition
- Medications- secondary bone loss
- Lack of efficacy to existing therapy



Monitoring:

Conventional

- Postmenopausal osteoporosis/ primary

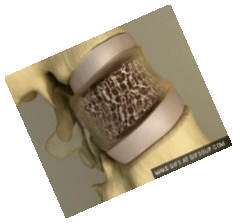
BMD – 0, 2 years

- Steroid induced osteoporosis

BMD – 0,1,2 years

New

For 5 years of treatment with BP or Denosumab monitoring of BMD is not necessary, according to new clinical guidelines from ACP.

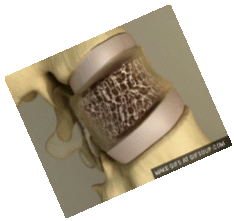


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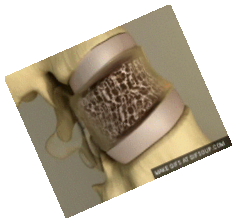
LSC:

- Least significant change calculated in BMD with gm/cm^2 , not in T or Z score
- Expected 6% or more
- Stable or <4% decrease



Challenges & controversies

- Impact of osteoporosis is high.
- Underlying pathology – still in innovation.
- Racial variation of peak bone mass not known.
- DEXA measurement is not available everywhere.
- Expensive drugs.
- No pharmacologic agent can effectively increase both non-spine and spine BMD.
- OP vs Osteomalacia.



Take home messages -



- OP is under recognized & under treated, in postmenopausal and Geriatric populations.
- Diagnostic Tools would be (BMD & FRAX)
- Non Pharmacologic therapy- Vit. D & Ca. supplementations
- Pain management.
- Currently approved drugs are HRT, SERM, Calcitonin, PTH, Bisphosphonate, Denosumab, Romosozumab.
- BP is foundation therapy despite all controversies Zoledronic acid is best.
- Newer drugs - Cathepcin K inhibitor-Odanacetib, oral PTH, oral Calcitonin, Icariin.
- Sequential therapy is new theme to combat OP.

Thank you !

